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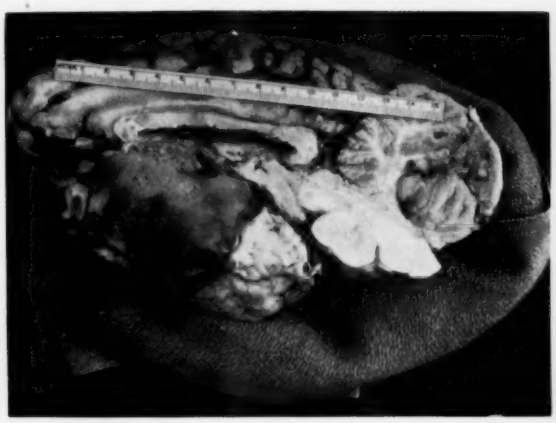

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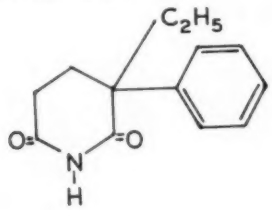
An Electroencephalographic Study of Doriden

HAROLD A. LADWIG, M.D., Omaha

The electrical activity of the human brain has been utlized to study the effect of several medications. The sedative medications, in particular, lend themselves readily to laboratory study with the use of the electroencephalograph. Such medications produce a relaxed state of the patient and reduce the artifact recorded as the result of outside stimuli. These medications, in addition to the production of sleep, frequently produce changes of the electroencephalogram. The alterations of cortical activity have been reported by other authors.*

The present study concerns the use of Doriden as a sedative compound.† The purpose of this particular study was to test the efficiency of Doriden as a daytime sedative. In addition to the study of its sedative properties, the effect on the electrical activity of the cortex following the ingestion of the medication was also observed by the use of the electroencephalograph.

Doriden is a nonbarbiturate sedative compound. It is a glutarimide and has the chemical name α-ethyl-α-phenyl glutarimide. Its structural formula is:



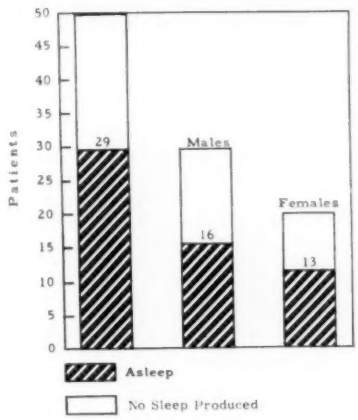


Chart 1.—Results for 50 patients receiving orally 500 mg. of Doriden.

Doriden is a white crystalline compound with a melting point of 83-85 C and possesses a molecular weight of 217.3. It is relatively insoluble in water but easily soluble in alcohol and acetone. During investigation of several compounds with anticonvulsant properties, it was discovered that a substance, Doriden, markedly depressed the central and autonomic nervous systems. Although classified as a short-acting hypnotic, Doriden is capable of producing deep, restful sleep. According to the studies by Blackwell,‡ a restful sleep may

Submitted for publication June 24, 1955.

Department of Neurology and Psychiatry, Creighton University School of Medicine.

* References 1 to 4.

† This project was aided by a grant from the Ciba Pharmaceutical Products, Inc. The Doriden (glutethimide, Ciba) used in the study was furnished by the Ciba Pharmaceutical Products, Inc.

‡ Blackwell, R. C.: Unpublished data.

be produced even in elderly patients which may carry them through the night.

METHOD OF STUDY

The patient was placed in bed in a soundproof, darkened room, and the EEG electrodes were applied. The patient was given an oral dose of 500 mg. of Doriden. The cortical activity of the patient was then recorded with the use of a Grass electroencephalograph.

A total of 50 patients were included in this study. Of the 50 patients studied, 40 were normal controls, free of suspected brain pathology; 10 were suspected of having some type of cortical dysrhythmia. The results of the study are recorded in Chart 1.

RESULTS

Of the 50 patients studied, sleep was obtained in 29, or 58%. The patients were able to go to sleep either at the time of the recording of the electroencephalogram or immediately after their return to the ward. Most of the patients slept for less than two hours; however, one patient slept for a period of eight hours after receiving the medication. A group of 100 patients who had received 100 mg. of secobarbital (Seconal) orally were studied under similar conditions in this laboratory.§ After receiving this amount of secobarbital, sleep was produced in 53 of the 100 patients, or 53%.

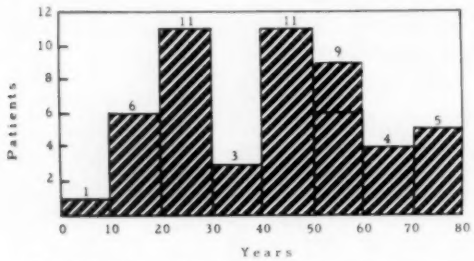


Chart 2.—Age distribution of 50 patients receiving oral Doriden.

Chart 1 also indicates the sex of the patients in the study; 30 of the total number tested were males and 20 were females. Sleep was obtained in 13 of the 20 females, or 65%, whereas only 16 of the 30 males, or 53%, were able to go to sleep with 500 mg. of Doriden. The ages of the group varied from 7 to 77; the breakdown of the age distribution by decades is shown in Chart 2.

The electroencephalograms which were obtained were studied carefully for any alteration of cortical activity following the ingestion of 500 mg. of Doriden. Certain changes normally are noted in the electroencephalogram as the patient goes from the waking state into the state of sleep. With the induction of sleep the normal 8- to 12-per-second electrical activity of the brain disappears and is replaced by regular 3- to 5-per-second waves.[5] This is followed by the occurrence of sleep spindles with 14-per-second activity, described by Loomis, Harvey, and Hobart.[6] Figure 1 illustrates the normal 8- to 12-per-second activity of the waking state.

Abnormalities were noted in 13 of the 50 records studied. The records of the normal, or control, group showed abnormalities in but 5 of the 40 records, whereas in the group with suspected abnormalities 8 of the 10 records were abnormal. These abnormalities included slow activity and spike activity, which varied from a focal to a diffuse ab-

§ Ladwig, H. A.: Unpublished data.

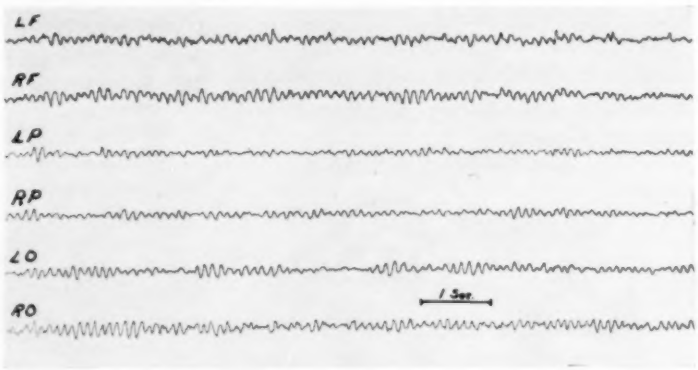


Fig. 1.—A six-channel electroencephalogram of a normal patient recorded during the waking state.

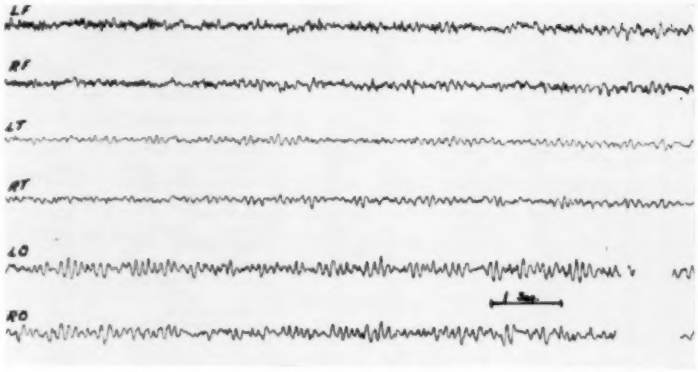


Fig. 2.—Fast activity seen chiefly in the frontal areas, following the ingestion of 500 mg. of Doriden.

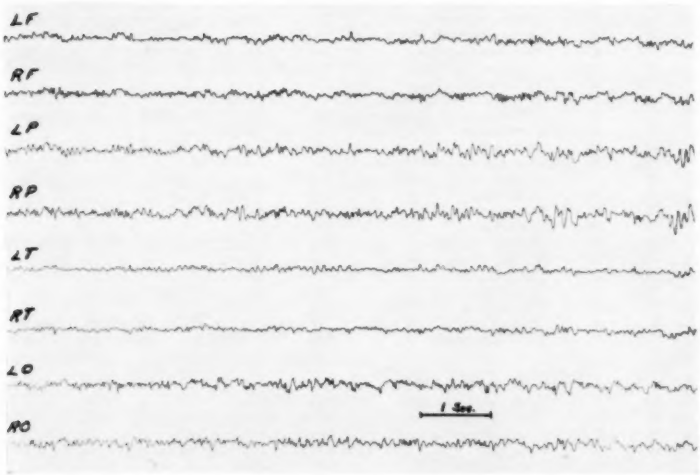


Fig. 3.—An electroencephalogram showing the presence of fast activity in the frontal and parietal areas after the ingestion of secobarbital (Seconal), 0.1 gm.

normality. These abnormalities were thought to be associated with actual cortical pathology or the presence of abnormal cortical activity in a so-called normal person.

Aside from the above-noted changes in the EEG, another alteration of cortical activity was observed. This alteration consisted of bursts of 20- to 30-per-second, fast activity with voltages ranging from 25 to 100μv, as is seen in Figure 2. This change was noted in 41 of the 50 records, or 82%. The presence of this cortical alteration after the ingestion of Doriden was thought to be due to the effect of this medication. This fast activity has been noted in the EEG's of patients who have received other sedative medications, namely, secobarbital and chloral hydrate.‖ This is seen in Figure 3.

‖ References 1 to 4.

On the day following the study, each patient was asked whether or not he had experienced any unusual symptoms following the taking of the medication. This was done in an unobtrusive manner. The results are tabulated in the Table. Fourteen of the total number complained of symptoms other than sleep. These symptoms included a feeling of grogginess and extreme lethargy, and some patients reported that they felt as if they had been drugged. One patient was very talkative for a period of three hours.

COMMENT

It was noted by Brazier and Finesinger[3] that intravenous injection of amobarbital (Amytal) sodium, thiopental (Pentothal) sodium, and pentobarbital sodium produced a characteristic alteration of cortical activity.

Results of Doriden Medication

	Name	Wt., Lb.	Race	Age, Yr.	Sex	Diagnosis	Sleep	Reaction
						Control Group		
1	B. M.	148	White	47	M	Hodgkin's disease	No	None
2	D. D.	144	White	65	M	Syncopal attack	No	None
3	H. S.	145	White	49	M	Depressive reaction	Yes	None
4	J. L.	136	Indian	66	M	Hypochromic anemia	Yes	Slept 1 hr. after return to ward
5	J. C.	130	White	29	M	Functional chest pain	Yes	Groggy 2 hr.
6	A. L.	132	Negro	22	M	Hemorrhoids	No	Drowsy 1 hr.
7	A. L.	112	White	54	M	Hemorrhoids	Yes	None
8	F. D.	106	Negro	65	F	Diabetes	Yes	Slept 1 hr. after return to ward
9	G. W.	137	Indian	23	F	Pyelonephritis	Yes	None
10	V. L.	102	White	25	F	Rheumatoid arthritis	Yes	Slept 2 hr. after return to ward
11	C. D.	114	White	19	F	Lupus erythematosus	Yes	Giddy and talkative 3 hr.
12	M. G.	196	Negro	49	F	Ulcer	Yes	Groggy, slept 8 hr.
13	M. G.	102	Indian	17	F	Psychoneurosis	No	None
14	S. W.	115	White	17	F	Conversion reaction	Yes	None
15	L. H.	120	White	43	F	Rheumatoid arthritis	No	Drugged feeling 6 hr.
16	A. M.	128	White	28	F	Neurodermatitis	Yes	Slept 2 hr.; then talkative for 1 hr.
17	C. M.	106	White	46	F	Hypertension	No	Felt tipsy for ½ hr.
18	W. G.	150	Negro	43	M	Brucellosis	No	Drowsy 1 hr.
19	O. M.	151	Negro	50	M	Lung abscess	Yes	Slept 1 hr. after return to ward
20	D. P.	107	White	14	F	Lupus erythematosus	Yes	Slept 2 hr. after return to ward
21	L. H.	123	Negro	42	F	Cardiac disorder	No	None
22	P. N.	132	Negro	37	F	Cardiac disorder	Yes	Slept 1½ hr. after return to ward
23	C. E.	133	White	44	M	Cardiac disorder	Yes	Slept ½ hr. after return to ward
24	H. W.	134	White	53	M	Nutritional edema	No	None
25	L. B.	127	White	26	M	Ectodermal dysplasia	No	Drowsy 1 hr.
26	H. B.	198	Indian	59	M	Guillain-Barré syndrome	Yes	Slept 1 hr. after return to ward
27	J. C.	112	White	74	M	Carcinoma of G.I. tract	No	Sleepy 1 hr.
28	W. J.	155	Negro	56	M	Diabetes	No	None
29	C. M.	155	White	54	M	Rheumatic heart disease	No	Sleepy ½ hr.
30	F. S.	116	White	67	M	Bronchogenic carcinoma	Yes	Sleepy ½ hr.
31	G. W.	192	Indian	44	M	Diabetes	Yes	Sleepy ½ hr.
32	H. B.	130	White	54	F	Psychoneurosis	No	Sleepy 3 hr.
33	P. L.	171	Negro	73	F	Diabetes	Yes	None
34	P. N.	108	White	31	F	Cardiac disorder	Yes	Slept 2 hr. after return to ward
35	O. S.	181	White	53	M	Myelogenous leukemia	Yes	None
36	A. T.	150	Negro	54	F	Sarcoidosis	No	None
37	A. S.	160	White	40	M	Hypertension	No	Groggy ½ hr.
38	A. S.	140	White	77	M	Pneumonia	No	None
39	T. F.	140	White	25	M	Bronchitis	Yes	Slept 2 hr. after return to ward
40	M. A.	103	Indian	74	F	Cholelithiasis	Yes	Slept ½ hr. after return to ward
						Suspected Abnormal Group		
1	D. D.	208	Indian	20	M	Convulsive disorder	Yes	None
2	N. W.	178	Indian	30	M	Convulsive disorder	No	Sleepy 1 hr.
3	E. A.	135	Negro	28	F	Convulsive disorder	Yes	Dizzy 3 hr.
4	M. B.	140	Negro	14	M	Epilepsy	Yes	Dizzy ½ hr.
5	T. C.	162	Indian	47	M	Head injury	No	None
6	D. S.	185	White	29	M	Brain tumor	Yes	None
7	F. M.	50	White	7	M	Seizures	Yes	Slept 2½ hr., groggy 4 hr.
8	H. J.	175	White	74	M	Brain syndrome, chronic	No	None
9	T. K.	121	White	28	F	Convulsive disorder	No	None
10	R. L.	120	White	14	M	Head injury	Yes	Sleepy 3 hr.

These investigators, after their study of the action of barbiturates on the cerebral cortex, reported that these medications produced an alteration of the cortical activity; the alteration noted was the presence of 21- to 32-per-second, fast activity with voltages ranging from 25 to 100μv in the recorded electroencephalograms of their patients. When the medication was given intravenously, this fast activity appeared first in the frontal leads, then spread to the parietal leads, and finally was seen in the occipital areas.

This action of the barbiturates on cerebral activity has been suggested by other investigators as being due to two effects. One is the change in the permeability of the cell membranes, and the other may be the interference with the dehydrogenase systems. As early as 1912, Lillie [7] concluded that the barbiturates caused an alteration of the surface membranes of the cell and subsequently there occurred an alteration of intracellular respiration, the reactions within the cell being governed by the surface condition of the cell.

Quastel,[8] in his excellent study, demonstrated that narcotics, even in a very low concentration, inhibited the oxidation of *d*-glucose, lactic acid, and pyruvic acid in vitro. In the process of brain metabolism, normally the principal substrate *d*-glucose is oxidized

through a long chain of intermediary reactions to carbon dioxide and water. With this, there is a liberation of a large amount of energy. In the first part of the breakdown of *d*-glucose, there is formed lactic acid, which is, in turn, oxidized to pyruvic acid. The dehydrogenase activity, which is necessary for the activation of lactic acid, and, in turn, for the production of pyruvic acid, is inhibited by the action of the barbiturates. The narcotics inhibit this dehydrogenase activity, presumably by forming surface films or absorption compounds which prevent the access of hydrogen donators to their activating enzymes.[9] The access of oxygen to the cells is unimpaired, but the oxidizing activity of the cell is diminished as a consequence. In turn, then, there is a depression of normal cellular activity, and thus a narcosis results.

Hubbard and Goldbaum,[10] in their studies with thiopental, stated that thiopental was found to inhibit oxidation of glucose, lactic acid, and pyruvic acid in vitro, but they observed no difference in the degree of inhibition between the control mice and the drug-tolerant mice. It was their conclusion that the in vitro depression of brain respiration by barbiturates cannot be the sole mechanism responsible for barbiturate hypnosis.

The chemical alteration of cortical activity with Doriden is, as yet, unknown. Other investigators have studied the sedative action of the medication. In a group of 20 patients suffering from chronic insomnia, Arms ¶ reported that even when larger than recommended doses (500 mg.) of Doriden were administered, the after-effects of the medication were minimal and the patients were able to work the following day without any feeling of depression or confusion. Goldner # studied a group of 48 patients with chronic psychiatric disabilities. These patients were given the medication for a period of 6 to 10 weeks. Complete blood counts and urinalyses were taken weekly on every patient; thymol turbidity and cephalin flocculation studies were performed on 22 patients. No patient revealed evidence of toxic effects of the blood or liver during this course of treatment with Doriden.

¶ Arms, A. V.: Unpublished data.

Goldner, M. G.: Unpublished data.

SUMMARY

The sedative action of Doriden was studied on 50 patients. With a uniform dose of 500 mg., sleep was obtained in 58% of the patients studied. The effect of this dose of the medication compares with the sedative action of 100 mg. of secobarbital (Seconal).

Several medications have been utilized to find the ideal sedation for sleep recordings of the electroencephalograms. The study revealed that Doriden produces an alteration of the sleep electroencephalogram similar to that seen with secobarbital and chloral hydrate. Thus, the search continues for an ideal sedation which does not produce any alteration of the sleep recording of the electroencephalogram.

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Acceptability for Psychotherapy in Institutionalized Narcotic Addicts

ALAN McLEAN, M.D.
JACK MONROE, Ph.D.
STANLEY YOLLES, M.D.
HARRIS HILL, Ph.D.
and
H. ALAN STORROW, M.D., Lexington, Ky.

At this hospital drug addiction is assumed to be a psychiatric problem. It is commonly held by psychiatrists that drug addicts are exceedingly difficult to treat. Fenichel,[1] among others, lists the addictions along with the perversions as the least susceptible of all nonpsychotic disorders to psychoanalytic therapy. Also, Dollard and Miller,[2] approaching the problem from the frame of reference of learning theory, suggest that the use of drugs is effective in reducing drives, thus leaving the patient less motivation for therapy.

At the present time only a small percentage of patients admitted to the U. S. Public Health Service Hospital at Lexington, Ky., can be provided psychotherapy. Therefore, if addict patients differ in acceptability for psychotherapy, a selection problem may exist, and it would appear desirable to select for psychotherapy those patients who are more acceptable for such therapeutic techniques.

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From the U. S. Public Health Service Hospital.

The following persons assisted in planning or executing the project: Kenneth Chapman, M.D.; James Crecraft, M.D.; William Ferguson, B.A.; Arden Flint, M.D.; James Grider, M.D.; Alan Holt, M.S.S.W.; Sherman Keiffer, M.D.; John O'Donnell, M.A.; Donald Painting, M.A., and Robert Rasor, M.D.

The purposes of the study were (*a*) to isolate patient characteristics which influence the psychiatrists' judgments of acceptability, (*b*) to estimate the percentage of a defined addict population that might be considered acceptable for psychotherapy, and (*c*) to determine the extent to which acceptability can be defined in terms of measures derived from psychological and sociological materials. The objective was, in part, to develop a uniform screening procedure to increase the likelihood of selecting acceptable patients for therapy.*

SUBJECTS

Patients in this study were limited to males from Northeasten metropolitan communities of 200,000 population or larger. The study was also limited to voluntary patients, committed volunteers, i. e., patients committed by a local Kentucky court for a period of four and a half months, and to Federal probationers, who were also at the hospital for a like period. In order to make the group more homogeneous, the sample was further screened as follows: (*a*) No patient who had been in the hospital more than four previous times was accepted; (*b*) patients studied were between 18 and 45 years of age; (*c*) no patient was utilized who began his use of narcotic drugs because of a medical problem; (*d*) illiterates and non-English-speaking patients were excluded.

From March 1, 1954, to May 28, 1954, a total of 205 patients met the initial requirements. Fifty of these left the hospital before starting the procedures. One hundred fifty-five patients were still hospitalized approximately one week following withdrawal from drugs and were assigned to the study. Of this

* This study was executed as a preliminary project to develop information and criteria to facilitate future evaluation of therapeutic programs of this hospital.

group, 100 patients completed the requisite assessment procedures and constituted the sample utilized in this study. The racial composition of the sample was 81% Negro and 19% white.

Since this group was not a random sample of all hospital admissions, generalizations from this study can be made only to future groups of patients that are selected in the described manner. It should be pointed out, however, that, while this was not a representative sample of institutionalized narcotic addicts, it was a defined sample of therapeutic candidates. Thus, except for the fact that Federal prisoners and certain other well-defined subgroups of patients were excluded, this sample was fairly representative of the population of addict patients from Northeastern metropolitan communities who remain in the hospital a sufficient length of time to become screening problems.

PROCEDURES

Subjects were evaluated, first, by a specially devised social service questionnaire; second by a psychiatric social worker's interview; third, by a battery of psychological procedures; fourth, by judgments of a board of staff psychiatrists, and, fifth, by a brief "trial period" in psychotherapy. The psychiatrists were primarily concerned with one factor, the degree of acceptability for psychotherapy. The therapist's judgment concerning acceptability became the criterion with which the psychological tests, the social service interview, and the social service questionnaire were correlated.

Each patient was started on the various procedures approximately one week after the withdrawal from narcotics was completed, and all procedures were carried out during the following, carefully scheduled, two-week period. The first week was devoted to social service evaluations and psychological testing, and the second week, to psychiatric board examination and the "trial period" in therapy. Processing was completed on each subject by the 29th day of his hospitalization. The procedures will be discussed in the order of their completion.

1. *Social Service Interviews.*—The patient's first contact with the study was through an initial social service interview, in which a questionnaire was completed.† The questionnaire covered information concerning the following: education, employment, military service, marital history, family history, antisocial history, religion, early group experiences, use of drugs, and plans for the future. The completed questionnaires were reviewed by a second psychiatric social worker, and he, without other information, arrived at an independent estimate of each patient's potential suitability for psychotherapy. Each item of the questionnaire was given a positive or negative rating, and the composite score for each area, composed of responses to several items, was correlated with the therapist's decisions concerning acceptability of the patient.

The second interview was conducted by a third psychiatric social worker, who rated each patient on 17 areas of previous adjustment while carrying out a relatively unstructured procedure. The first, and usually the major, part of the interview was devoted to the development of a permissive atmosphere, and only toward the latter part of the interview was the patient asked questions relating to the specific points which would be evaluated. Areas covered included social history, such as educational adjustment and employment stability, sexual adjustment, family background, and stability of childhood adjustment, as well as the patient's present motivation for therapy. The psychiatric social worker recorded an independent estimate of each patient's acceptability for therapy, and these predictions were compared with the therapist's judgments when the study was completed.

2. *Psychological Testing.*—A battery of psychometric tests was administered. Some of these were given to patients in groups; others were administered individually. Most of the group tests were self-rating questionnaires of habits, attitudes, and feelings. One of these was the Minnesota Multiphasic Personality Inventory,[3] and the others were two experimental questionnaires. One questionnaire was composed of 120 items taken from the Thurstone Temperament Schedule [4] and the Wesley Rigidity Scale [5]; the other, the Hill Personal Inventory,‡ was designed specifically for the study. The Cornell Medical Index [6] was given individually following the administration of the Wechsler Bellevue Intelligence Examination.[7] The Oral Directions Test,[8] a phonographic recording of a 30-minute intelligence test, was administered to patients in groups. However, mechanical failure in the administration of this test led to its being discontinued before the study was completed. In addition to these procedures, the Rorschach Test [9] and the Human Drawings Test [10] were administered to 92 of 100 subjects, but results of these projective techniques will not be included in the present report.

Two approaches were taken in the analysis of the self-rating inventories. First, various subscale scores

† A copy of the questionnaire can be obtained by writing the Medical Officer in Charge, U. S. P. H. S. Hospital, Lexington, Ky.

‡ Hill, Harris E.: Unpublished self-rating questionnaire. Information concerning this psychometric instrument can be obtained from Dr. Hill, Senior Research Psychologist, NIMH Addiction Research Center, U. S. P. H. S. Hospital, Lexington, Ky.

were computed and correlated with the criterion measure of acceptability. On the Hill Personal Inventory, since no a priori scoring keys were available, a second method of analysis was necessary. An item count was made to isolate the items which were significantly related to the criterion. This was done on a random half of the over-all sample. An empirical scoring key was constructed to reflect the direction of response (true or false) of the group of acceptable subjects. The personal inventories of the remaining half of the subjects were then "scored" for degree of acceptability, and group differences between the more acceptable and the less acceptable subjects were tested for statistical significance. A similar cross-validation procedure was performed on the MMPI.

In the analysis of psychometric tests, each subtest of the Wechsler-Bellevue Scale was correlated with the criterion. Each of the three I. Q. equivalents (Bellevue Weighted Scores) were similarly analyzed. In addition to these, various qualitative and quantitative indices were computed from the Bellevue protocol, and the differences between their respective frequencies in the two groups were tested for statistical significance. The Oral Directions Test was analyzed for the first 50 subjects.

3. *Psychiatric Board Interviews.*—The first 66 consecutive patients were interviewed for a period of 20 minutes by a board of three psychiatrists, none of whom acted as therapists in the study. At the conclusion of the interview, which was in the nature of a semistructured, question-and-answer period, each member of the board was asked to classify independently each patient as acceptable or less acceptable for psychotherapy. Since there was insufficient agreement among members of the board, this procedure was discontinued after two-thirds of the patients had been seen. It was not practicable for the board to invest longer periods of time in observation; had this been done, there would doubtless have been closer agreement.

4. *Psychotherapists' Evaluation of Acceptability for Psychotherapy.*—Each patient received a "trial in therapy" of three interviews conducted by one of three psychiatrists who had had similar training and experience in the treatment of addicts. An effort was made to analyze the interpersonal relation of the patient and the therapist as it developed and to base the decision concerning acceptability primarily upon this developing relationship. While each interview was approximately 50 minutes in length, the therapist was free to terminate an interview after a shorter time if it seemed advisable. If he felt the relationship showed signs of becoming a successful therapeutic one, the patient was considered acceptable for therapy. During each session the therapist made two sets of brief notes, one concerning problem areas raised by the patient and the other concerning the therapist's reaction to the situation at the time. While the therapists were not asked to base their decisions concerning acceptability on a particular pattern of patient response, a series of questions to be answered "yes" or "no" concerning each patient was used to guide the evaluating process.§

Since the optimal length of hospitalization for voluntary patients has been determined by the staff as a four-and-a-half-month period, therapy is of necessity a short-term process. Psychotherapy at this hospital with voluntary patients averages 20 to 30 hours, with the major goal usually that of motivating the patient to seek further treatment after discharge. It is necessary, therefore, to make a decision within the first month of hospitalization as to whether thserapy will be offered. In the absence of controlled observations of patients over a long period, a brief "trial in therapy" was the only practical method of obtaining estimates of acceptability for the present study.

RESULTS AND COMMENT

The Criterion of Acceptability for Psychotherapy

The psychotherapists' evaluation of the 100 patients who completed all phases of the study resulted in their terming 46 as acceptable and 54 as less acceptable for therapy. Among the more significant reactions which therapists felt contributed to their judgments were (*a*) the patient's ability to verbalize feelings, as well as ideas (82% of the acceptable were scored positively, while only 21% of the less acceptable were so scored); (*b*) evidence of original thinking (90% acceptable, 43% less acceptable), and (*c*) spontaneous verbal production in problem areas (78% acceptable, 15% less acceptable).

The psychiatrists reported that 77% of the acceptable patients voiced evidence of emotional problems, as compared with only 7% of the less acceptable. Forty per cent of the acceptable group spontaneously asked

§ A list of questions used in the therapeutic evaluation can be obtained on request from the Medical Officer in Charge, U. S. P. H. S. Hospital, Lexington, Ky.

for help with their problems, whereas only 9% of the less acceptable group made this request. Questions relating to previous modifiability of behavior were particularly interesting. In the opinion of the therapists, 77% of the acceptable group gave evidence of previous ability to change patterns of living. In the less acceptable group 35% gave such evidence. The therapists assumed a directive role in only 6% of the acceptable group, whereas in 51% of the less acceptable group considerable structuring of the situation and a more active role were required of the psychiatrist. The therapists reported a liking for 95% of the acceptable group, while in the less acceptable group this occurred in 43% of the cases.

Factors which did not appear to differentiate between patients included the degree of attentiveness to the therapeutic situation and the degree of patient rejection of the therapist's ideas because of strong ideas of his own. It also seemed to make little difference whether or not the patient came to the hospital because of outside pressure.

Since each of the three therapists interviewed approximately one-third of the total sample, this question arises: How closely would they have agreed on their estimates of acceptability for therapy if they had each interviewed all patients? If the frames of reference employed by the psychiatrists in making their judgments were essentially different, there would be little reason to expect agreement between the outcome of this study and the outcome of others that were conducted in a similar manner. On the other hand, if it could be demonstrated that the therapists in this study employed essentially the same frame of reference in arriving at an estimate of acceptability for psychotherapy, it would be reasonable to assume that other psychiatrists with similar training and background, following similar procedures in assessing a comparable sample of subjects, would respond in like manner to the same patient characteristics.

The similarity of the percentages obtained on various response patterns, the means of which are given above, indicates that the therapists were basing their judgments on similar criteria. Stronger evidence of the community of judgments, however, is found by comparing each of the therapists' judgments of patients with the results of the psychological tests and social service evaluations. Regardless of which psychiatrist made the judgments, similarity was found between his estimates of acceptability and the predictions of the social workers and the psychologists. The psychiatric social worker who observed all patients was able to predict with a significant degree of accuracy the direction of judgment of each therapist taken separately. Similarly, regardless of which therapist had judged the subject acceptable, scores on personality tests which tended to characterize one acceptable patient tended to characterize another.

Social Service Evaluation

Specific areas covered by the questionnaire were significantly correlated with the criterion of acceptability for therapy. The items of the questionnaire dealing directly with the patient's motivation showed an agreement with the therapists' judgments in 66 of the 100 cases. Predictions from an overall evaluation of the questionnaire resulted in 65% agreement with the therapists on patients termed acceptable and in 71% agreement on patients termed less acceptable.

The social service interview produced agreement with the therapists in 70% of the patients labeled acceptable for therapy and in 75% of those labeled less acceptable. The staff member who conducted the psychiatric social service interview was of the opinion that he could classify the patients into three groups. In the first group were those patients who resisted the interview situation; they refused any attempt "to get to know them." These subjects were classed as less acceptable for therapy. Subjects of the second group, who seemed to possess characteristics the opposite of the first were very responsive. They participated actively and quickly, and were as readily classed as ac-

ceptable for therapy as the members of the first group were classed as less acceptable. A third group was considered borderline. These patients were able to respond and participate, but on a minimal level. Judgments of acceptability of this group were about equally divided.

Psychological Evaluations

The inventory of Habits and Attitudes and the Cornell Medical Index failed to show reliable differences between the two criterion groups and will not be mentioned further. Results of the projective tests will be reported in a later study.

The average Wechsler-Bellevue scattergrams for the two groups showed that the acceptable group was uniformly superior on all subtests. On the vocabulary, information, and comprehension subtests of the verbal scale, differences between the groups were statistically significant. The patterns of the scattergrams of the two groups, however, were nearly identical.

The MMPI, as a multivariate instrument, provides a pattern, or profile, which is useful in clinical descriptions of personality. The differences on one clinical scale (Masculine-Feminine) and on one experimental scale (Taylor-Anxiety) reached statistical significance. The mean profile of the acceptable group on this inventory was somewhat more deviant on nearly all scales, but the general personality pattern was strikingly similar for the two groups.

The item count of the MMPI yielded significantly more predictors of acceptability than would be expected on the basis of chance. A scale composed of these items would refer a group of patients, 66% of whom would prove acceptable for therapy.

Item analysis of the Hill Personal Inventory permitted the construction of an empirical Acceptability Scale composed of 29 items, which would agree with the judgment of the therapists in 74% of all cases.

One of the most striking findings is the marked similarity in the personality profiles or patterns which characterize the two groups of subjects. Differences in personality seem to be differences in degree rather than differences in kind. This is especially true in the way the subjects perform on the self-rating questionnaires. One possibility is that the two groups have great community of responses or behavioral equipment and are mainly distinguished by certain attitudes concerning their own behavior. That the two groups are quite similar is beyond question. Previous studies and the present one showed that much similarity of MMPI and Wechsler-Bellevue profiles is obtained, irrespective of how the hospitalized addict population is sampled. It may well be, then, that the main difference between the acceptable and the less acceptable patients is based upon divergence in self-evaluations of their personal and interpersonal reactions.

Percentages of Agreement of the Various Procedures with the Therapists' Judgments of Acceptability

Screening Procedures	Agreement on Acceptable Patients	Agreement on Less Acceptable Patients	Total Agreement
Brief scale from the MMPI (31 items)	66	62	64
Verbal score from the W-B Intelligence Scale	69	63	66
Social service data (blind interpretation)	65	71	68
Social service evaluation (hour interview)	70	75	72
Hill Acceptability Scale (29 items)	70	77	74

Relative Efficiencies of Screening Procedures

The percentages of agreement of the various screening procedures with the therapists' judgments of acceptability shown in the Table were significant beyond the 0.05% level of confidence.

The best single predictions were provided by the psychiatric social worker's hour interview and the Hill Personal Inventory. The inventory was more economical than the interview, since it was administered to patients in groups. Furthermore, if the Acceptability Scale from that inventory was used to refer to therapy those patients scor-

ing in the upper quartile, 78% of such referrals would prove acceptable for psychotherapy as judged by present criteria. Finally, combinations of the various screening procedures could be utilized to increase materially the likelihood of selecting groups of patients composed only of acceptable subjects. The Acceptability Scale and the psychiatric social worker's hour interview, for example, were used in combination to select, from the total sample, a subsample of patients, 89% of which was judged to be acceptable for therapy.

Implications of the Study

The study indicates that, by formalizing the interview procedure, the psychotherapists based their judgments of acceptability on similar criteria. The results show that various consistent patterns of patient personality characteristics were influential in forming judgments.

The results demonstrate that social service interviews and psychological methods can select a sample of subjects from a larger population which is very similar to that which psychiatrists, after a brief trial, consider to be acceptable for psychotherapy. Furthermore, this can be done economically in terms of time and quantity and quality of effort. Whether these are practical implications will depend upon what uses can be made of such samples of subjects. Experimental groups of subjects for future research studies could be drawn using screening procedures derived from this study. Also, certain of the screening tests and procedures could be used as part of a psychological test battery, to facilitate the decision to treat or not to treat in the case of individual patients.

Summary

The purpose of this investigation was to study the possibility of developing a screening procedure for selecting patients for psychotherapy, to attempt isolation of patient characteristics by which psychiatrists judge acceptability for such therapy, and to obtain an estimate of the percentage of addicts who would be termed acceptable for psychotherapy.

Consonant with these purposes, 100 institutionalized addict patients were individually interviewed for three hours in an effort to isolate those that would be more acceptable for psychotherapy. To determine personality characteristics and sociological data that would differentiate the acceptable from the less acceptable, a battery of psychological tests, a social service questionnaire, and a detailed psychiatric social service evaluation were completed on each patient.

Judgments of acceptability were made by three psychotherapists, who each interviewed approximately one-third of the sample. Acceptability so judged was the criterion with which all other estimates were correlated.

Forty-six per cent of the sample of narcotic addicts studied were considered acceptable for psychotherapy. The patients' ability to verbalize feelings, spontaneously produce problems for discussion, and give evidence of original thinking appeared to be significant in placing the patient in the acceptable group. Patients in this group were also more apt to ask for aid with their problems, and showed more evidence of previous ability to modify their patterns of living.

Estimates of acceptability made by psychiatric social workers based upon a formal social service questionnaire, as well as on the unstructured hour interview, correlated significantly with the psychotherapists' judgments. Certain psychological measures, including tests of verbal intelligence and degree of manifest anxiety, were significant predictors of acceptability. Finally, various combinations of screening procedures demonstrated that patients judged to be acceptable for therapy by psychiatrists could be selected from a larger group of patients by social service interviews and psychological tests with a high degree of accuracy.

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Efficacy of Chlorpromazine in Hyperactive Mentally Retarded Children

H. V. BAIR, M.D.
and
WILLIAM HEROLD, M.S., Parsons, Kan.

The following study, investigating the effect of chlorpromazine (Thorazine) on hyperactive mentally retarded children, was made at the Parsons State Training School, Parsons, Kan. The subjects selected for the study represented, in the opinion of the entire staff, the 10 most hyperactive students at the Training School. Their behavior was characterized by temper tantrums, boisterousness, fighting, overactive antics, and sometimes destructiveness to property. These students could not seem to make the minimum adjustment to their classroom tasks, their job placements, or their cottage life. A control group of 10 students was also selected and matched with the experimental group according to age, sex, and I. Q.

The subjects in each group consisted of seven male students and three female students. The ages ranged from 7 years 7 months to 20 years 3 months, for the experimental group, with a mean of 13 years 2 months. The control group's age range was 7 years 4 months to 20 years 3 months, three having a mean of 13 years 1 month.

Each subject was administered an intelligence test Jan. 7, 1955. The test used was the Columbia Mental Maturity Scale. Results of the test indicated that on Jan. 7 the I. Q.'s for the experimental group ranged from 22 to 83, with a mean of 53.7. The I. Q. range of the control group was 23 to 90, with a mean of 53.5. The I. Q. range of the control group was 23 to 90, with a mean of 53.5.

Chlorpromazine * was administered to each student of the experimental group (25 mg. t. i. d., taken orally) each day for 60 days. During the two-month period, Jan. 7 to March 7, 1955, the cottage aides, school teachers, therapists, and medical staff made observations as to the students' behavior. Weekly reports were submitted by these observers, which, in turn, were compiled for a final evaluation.

On March 7, the students were retested. The results indicated that the I. Q. range of the experimental group was then 30 to 108, with a mean of 64.1—an average increase in I. Q. of 10.4 points per student.

The test results also indicated that the I. Q. range of the control group on March 7 was then 26 to 88, with a mean I. Q. of 56.0 —an average increase in I. Q. of 2.5 points per student. The difference between the mean increases in I. Q. in the two groups is statistically significant at the 1% level of confidence.

An examination of the weekly reports submitted by the observers as to the students' behavior indicated that seven students showed vast improvement, two improved favorably, and one showed no significant improvement.

Aside from the over-all improvement in mental functioning as indicated by the intelligence test results, it was found that each student slept better at nights, quieted down

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* Chlorpromazine chemically is 10-(3-dimethylaminopropyl)-2-chlorophenothiazine. Medication for this study was furnished through the courtesy of Smith, Kline & French Laboratories, Philadelphia.

considerably, and followed instructions diligently.

Eight of the ten students frequently reported vivid dreams about their homes and their parents. Such dreams were never voluntarily revealed previously.

Changes in Intelligence Quotient with Chlorpromazine Therapy

Subject	Sex	Age	I. Q. (1/7/55)	I. Q. (3/7/55)	I. Q. Change
Experimental Group					
A	M	7-7	76	82	6
B	M	9-1	36	45	9
C	F	9-4	66	69	3
D	F	10-10	22	30	8
E	M	13-1	45	66	21
F	M	13-5	45	59	14
G	F	15-2	50	53	3
H	M	15-10	83	108	25
I	M	16-10	37	49	12
J	M	20-3	77	80	3
Group mean		13-2	53.7	64.1	10.4
Control Group					
A	M	7-4	72	70	−2
B	M	8-9	43	48	5
C	F	9-4	62	66	4
D	F	11-2	23	26	3
E	M	13-1	48	48	0
F	M	13-10	51	55	4
G	F	15-0	53	58	5
H	M	15-6	90	88	−2
I	M	16-9	30	35	5
J	M	20-3	63	66	3
Group mean		13-1	53.5	56.0	2.5

Six students stopped biting their fingernails; four continued. Nail biting appears to be a trait of the mentally retarded; in fact, it would be safe to state that 90% of the student population bite their nails.

Highly favorable reports were submitted on eight students by the teachers, therapists, and job supervisors. In general, the reports of these observers indicated a significant increase in the students' attention spans, which theretofore had practically been nonexistent.

Subject B, an extremely hyperactive boy, who seemed to be unable to control his primitive impulses, had the habit of standing on his tiptoes as he tensely but rhythmically extended and contracted his arms at the same time that he wiggled his fingers and rotated his wrists. This condition had existed most of his life but has now disappeared.

Subject H, a boy who was characterized by his fighting with other students, his rapid mood changes, and his destructiveness to property, has settled down to the point where he now holds a job behind the counter in the students' canteen. He is an excellent worker and appears to have taken on a new attitude toward life in general. His raise in I. Q. of 25 points was the most significant in that category.

The raise in I. Q. of the experimental group was phenomenal. This increase may be attributed to the removal of severe emotional and nervous disorders that had prevented the students from functioning at their true level of mental ability.

Laboratory tests on the experimental group showed no perceptible changes. The initial C. B. C. and urinalysis remained essentially the same throughout the course of treatment. Follow-up tests were made at three-week intervals. It may be stated, therefore, that there were no side-effects from the chlorpromazine therapy.

It may be concluded from this study that chlorpromazine is effective in its use with hyperactive mentally retarded children. The results of this study are extremely gratifying; however, more studies of this nature need to be made in order to test its reliability.

Parsons State Training School.

Psychologic Factors in Convulsive Disorders of Focal Origin

ERNST A. RODIN, M.D.
DONALD W. MULDER, M.D.
ROBERT L. FAUCETT, M.D.
and
REGINALD G. BICKFORD, M.B., Rochester, Minn.

Psychic phenomena as part of epileptic seizures have long been known to exist. It was not until the days of Bright, Todd, and Hughlings Jackson, however, that they were completely stripped of supernatural and magical connotations and put in a rational frame of reference.[1] With the description of "uncinate fits,"[2] impetus was given to research along anatomicophysiologic lines. The advent of electroencephalography and the studies of Penfield and Jasper,[3] as well as Gibbs and associates,[4] further established the temporal lobe as the main area of the brain which would give rise to psychic phenomena in seizures. These phenomena may take the form of visual, auditory, olfactory, or gustatory hallucinations; dreamy states; perceptual illusions; recollection of memories, or forced thinking. Penfield and Jasper's studies on the exposed cortex showed that all these experiences could be reproduced by cortical stimulation when they formed part of the particular patient's spontaneous attack. Furthermore, it was noted that some of the memories reproduced were "total memories" and included the feeling tone which was present at the time this particular engram was formed.

It was also noted by various investigators that patients with seizures of the temporal-lobe variety tended frequently to present in the interictal stage symptoms of a psychiatric nature in the form of hysteria, psychoneurosis, obsessive-compulsive personality traits, or frank psychotic episodes.*

Occasionally, a seesaw relationship was observed between seizures and the psychologic state. When the seizures could be brought under control by medication, the psychologic difficulties increased. They diminished when the medications were reduced and the patient was thus allowed to have some seizures again. It was also suggested that patients with this particular type of seizure tend to gravitate more toward mental institutions and epileptic colonies because of their asocial behavior and because they are supposedly more prone to develop the "epileptic personality."[9]

In general, research aimed at the understanding of the temporal-lobe type of seizures has been directed up to the present time mainly along descriptive lines. A number of excellent reviews are now available.† A variety of sensory, motor, and psychic phenomena which are prone to occur have been pointed out, as well as the electrophysiologic concomitants and the pathways involved in the spread of the seizure discharges.

We are now overwhelmed with a mass of clinical data which show some stereotypes in motor behavior (for example, chewing motions) or visceral autonomic sensations,

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Fellow in Neurology, Mayo Foundation (Dr. Rodin). Section of Neurology (Dr. Mulder); Section of Psychiatry (Dr. Faucett), and Section of Physiology (Mr. Bickford), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

* References 5 to 8.

† References 3, 4, and 10 to 14.

while there are other features of the attacks in which no two patients seem to be alike. Especially, some of the psychic experiences show a great variety. While there are, however, no similar syndromes in these seizure manifestations, the individual experiences during the onset of the seizure are, on the other hand, for the most part surprisingly constant, although it is known that some variants exist. This constancy of experiences raises, however, an important question. Why does this particular experience come up over and over again? A number of answers present themselves. It may be a haphazard occurrence because this particular engram happens to be stored in the particular spot where the focus of seizure activity is. Another possibility was suggested by Pötzl [14] as early as 1934, namely, that at the onset of a seizure the cortex finds itself in a hypersensitive state and visual or auditory experiences during that time may leave a deeper imprint than in the normal state and for this reason these perceptions may later be repeated in future spells as hallucinatory phenomena. A further alternative may be that experiences of that nature have a larger representation in the cortex of the patient in question because of emotional connotations which are significant to him.

As long ago as 1908 [15] Freud postulated that organic and structural explanations would eventually be found for all symbolic functions. The study of the relationship between structure and higher symbolic functions in the cortex has not been adequate, although recently papers by Kubie [16] and Ostow [17] have pointed out that it may be possible for neuroanatomic and neurophysiologic facts to be integrated with psychoanalytic theory. This is a very important area of research. Only by a more thorough study of patients with structural changes who manifest psychologic aberrations can we begin to develop an anatomy of fantasy and dream life and overcome the "organic-functional" dichotomy which now obscures this subject in controversy.

The study of these problems is handicapped by several factors: 1. These patients must necessarily be studied by a group, with the neurologist and neurophysiologist contributing their knowledge of structure and function, and the psychiatrist contributing his insight into symbology, unconscious mental activity, and dreams. It has sometimes been difficult for these different disciplines to devise a common language for identical phenomena. 2. The psychiatrist has not yet been able to devise a technique which allows him to understand the symbolic meaning of thoughts, fugues, or behavior without a protracted study of the patient's life. Not only is it necessary to collect a detailed history of the patient's life, but ideally time would be allowed for a transference relationship to develop and thus permit the elucidation of some repressed or unconscious material. The patients who fit the necessary criteria for this type of study often have a progressive structural change which demands a therapeutic intervention before the psychiatrist has had time to collect adequate data. The present study suffers markedly from this handicap.

We feel it worth while, however, to present reports of the following cases in spite of some inadequacy of psychiatric data in order to point out that a common approach by neurologists, psychiatrists, and neurophysiologists might well lead to a better understanding of a patient's symptom, which is otherwise bizarre and apparently devoid of meaning.

REPORT OF CASES

CASE 1.—A 44-year-old man experienced his first attack in early August, 1954. He awoke from a sound sleep with a dreamy sensation and a strange taste and smell. This lasted for only one minute, and he went back to sleep immediately. The next forenoon he had another attack, which consisted of a full feeling in the throat, "something like a belching sensation," and everything appeared to be like a dream, "just like a floating, hazy, and faraway feeling." Associated with this was a peculiar smell and taste which he had difficulty in describing, but it reminded him to some extent of pines. About the same time the patient's left hand became numb, like being asleep, and the right hand also, to a less extent. The entire spell lasted about one minute and was followed by some drowsiness. From that time on, the patient con-

tinued to have these attacks, in which he never lost consciousness. The frequency of the attacks ranged between 3 and 15 times a day. The patient made the point that the entire situation was pleasant and he was not afraid of the attacks. He never had a grand mal seizure. Further questioning in regard to the dreamy sensation led, after considerable hesitation on the part of the patient, to the statement that in addition to the floating, hazy sensation he had a visual hallucination, which consisted of watching a wrestling match. He saw two wrestlers fighting, one of them being a Japanese, the other somewhat nondescript; in the corner there stood a man who was somewhat short and kept talking all the time. The patient was unable to hear anything spoken, but he saw from the motions of the mouth of this person that he was talking.

The results of clinical neurologic examination and those of perimetry, the roentgenogram of the skull, and the resting electroencephalogram were all normal. With pentylenetetrazol (Metrazol) activation the taste and smell sensations that were usually associated with the patient's attacks developed. These sensations were accompanied in the electroencephalogram by diffuse rhythmic activity of 5 to 7 cycles per second in all head areas. This rhythm was then replaced by activity of 3 to 4 cycles per second, lateralized mainly to the right side; the occipital, parietal, and Sylvian areas were particularly involved. During the attack no clinical changes could be observed in the patient. The experience was entirely subjective.

Anticonvulsant medication was prescribed, and the patient was advised to return for reexamination in three months. When he returned, three months later, he stated that his spells had markedly decreased both in severity and in frequency. They consisted then only of faraway feelings of short duration, which were not associated any more with hallucinatory experiences. The results of clinical neurologic examination were still negative. Roentgenograms of the skull revealed, however, an intracerebral calcification in the right temporal region, and the resting electroencephalogram showed a delta focus in the right Sylvian region. Ventriculography and craniotomy were performed and revealed a friable malignant tumor deep to the middle meningeal artery on the right, and extending into the basal ganglia at the temporofrontal junction. In the tip of the temporal lobe, at a depth of approximately 3 cm., an area of calcified gliosis was discovered. Subtotal removal of the tumor and resection of the tip of the temporal lobe were carried out.

Psychologic Data.—This patient was an emotionally mature and stable person. A psychiatric investigation gave no evidence of emotional tension. The patient's main pleasures were outdoor sports, like hunting and fishing in the North Woods of Minnesota (pine area), and it was on one of these occasions that his first spell occurred. His favorite spectator sport was to watch wrestling matches on television. He did not care for baseball and football. Thorough questioning in regard to the particular Japanese wrestler whom he saw in his spell revealed that this was a wrestler he had seen repeatedly on television and the only wrestler he ever desired to see in person. He had been very much impressed with this particular wrestler and had taken a special trip over a considerable distance to see him. The trip was memorable because it was in midwinter and the roads were icy; nevertheless, the patient never regretted having had the opportunity to see this match.

Case 2.—A 64-year-old man had a meningioma of the right sphenoid ridge removed in 1950. The tumor had been sufficiently large to extend into the middle fossa, compressing also the temporal lobe. Three months prior to operation the patient had experienced grand mal seizures, which were not associated with an aura as far as he could recollect. After removal of the tumor the patient had no more attacks until 1953, when episodes of "an empty feeling in the head" began to develop. These were accompanied by a sound of music, as if he were in an orchestra pit. The attack was also associated with a pounding and throbbing sensation of the heart, and his color became pale. There was no description of automatic movements. The entire attack lasted one or two minutes.

The results of clinical neurologic examination were essentially normal. The roentgenogram of the head was also normal with the exception of a frontotemporal craniotomy on the right. The electroencephalogram showed a high-voltage, sharp-wave discharge in the right Sylvian area. In order to observe a seizure, pentylenetetrazol (Metrazol) activation was carried out. During this procedure there occurred a build-up in the right Sylvian area of rhythmic activity of 3 to 6 cycles per second, which frequently had the appearance of sharp waves. This discharge then spread to the entire right hemisphere, and the patient complained of a floating sensation at that time. After this, a rhythmic, high-voltage, sharp-wave discharge of 3 to 4 cycles per second occurred, limited to the right Sylvian area, and the patient stated at that time that he was hearing an orchestra playing. It was as if he were sitting in the theater in the third row and could see a golden stage curtain, and a timpani player toward the left field of vision. This was followed by the appearance of a blue light, and shortly afterward the spell ceased. It lasted altogether two to three minutes. Focal slow-wave activity persisted, however, in the right Sylvian area for some time afterward. During the spell there were no abnormal movements, and the patient was able to continue talking and to describe

the episode while it was happening. There was no fear associated with the spell. The situation, on the contrary, was rather pleasant.

Psychologic Data.—The patient was a mechanic in an aircraft factory. He held this position, however, only for economic reasons. His original and lifelong ambition had been to become a musician. He recalled many instances of his early youth, when he used to go to rehearsals in theaters in New York, especially to symphony concerts, as his main means of entertainment.

CASE 3.—A 23-year-old woman came to the Mayo Clinic because of "mixed-up spells" since the age of 6 or 7 years. She described these spells as "funny feelings in which my mind gets all mixed up." She said that during the spells she thought "of four or five things one after the other real fast, and they all get mixed up." There were "no particular thoughts" and nothing that she could "really explain." The thoughts, she stated, were neither pleasant nor frightening. The episodes lasted one to three minutes, after which she felt normal or had a little headache. During the episode her face flushed "as if all the blood rushes to the head." She felt hot all over; the fingers and arms tingled, and she had a feeling of the stomach turning over inside, as if she got "a sort of disappointed feeling." During these episodes she often had a sensation of something coming up through the throat which caused a smothering feeling. She had to swallow hard, and the heart felt as if it were beating rapidly. As a rule there was no loss of consciousness, but she thought that two or three times she might have lost consciousness altogether for a period of about one minute. These seizures occurred up to three or four times a day. There was no fear associated with the attacks. The patient attributed these seizures to excessive worry over early masturbatory experiences, in which she had indulged to an unusual degree about the age of 5 years. She had stopped masturbating at the age of 12 years but continued to have an ardent desire to do so and used to awaken frequently during the night, finding that she had masturbated in her sleep.

Since the age of 15 years the patient had had grand mal seizures; these were all at night with the exception of one, which occurred while she was at work. Preceding the grand mal seizures the patient experienced various dreams; then these dreams got all mixed up and she had a convulsion. The dreams were not always the same, but the feeling that the dreams got mixed up was the same as the feeling that the thoughts were getting mixed up during the day when the patient had the minor seizures. The patient had the grand mal attacks mainly in the period of falling asleep, and she was not certain whether she dreamed with all the seizures.

The results of clinical neurologic investigation and the roentgenogram of the skull were essentially normal. The electroencephalogram showed generalized dysrhythmic abnormalities consisting of medium- to high-voltage activity of 4 to 7 cycles per second, mainly in both temporal areas.

A sleep recording was obtained without premedication. During this period random slow-wave activity was seen in the right Sylvian area associated occasionally with high-voltage sharp-wave discharges. In the stage of light sleep, as judged by the electroencephalogram, the patient suddenly opened her eyes, made chewing movements with the jaw, tried to sit up, looked around bewildered, moved around and tossed on the bed, and was unresponsive. This attack lasted one minute; then the patient became responsive and stated that she had had a spell. She remained, however, confused for another minute; she tried to talk, but the speech was somewhat slurred and hardly intelligible. Finally she stated that she had had one of her convulsions, which was ushered in, as far as she could remember, by a dream. She stated that she had not been quite asleep, but almost. She saw huge trees, like a jungle, with big leaves. These were then all mixed up and seemed all around her. Then she felt as though they were closing in on her. Electroencephalographically, the seizure was characterized initially by some flattening of the recording and then high-voltage rhythmic activity in both Sylvian leads and, to a less extent, in the frontal area. The activity then took the form of atypical spike-wave discharges, maximal in the frontal areas. The spike components were more pronounced on the right than on the left and extended on the right side into the occipital region. During the period of mental confusion the recording was flat for a period of 10 seconds. Only in the Sylvian areas, again more pronounced on the right than on the left, some medium-voltage rhythmic activity occurred. After the seizure the patient was allowed to go to sleep and reached a medium-deep level of sleep without further incident. The sleep recording at this time was again characterized by some slow-wave activity and occasional sharp-wave discharges in the right Sylvian area and, to a less extent, in the right occipital area.

After the sleep recording the patient was unable to recall the dream which she had described immediately after she had come out of her seizure.

Psychiatric Data.—About the age of 5 or 6 years the patient had had bad dreams of her mother's being sick or dying. She would wake up during the night and cry, so that her mother would finally come and take her into the bed with her and the father. These dreams made the patient very uneasy for a period of three days following. These dreams would then come together in a mixed-up form at noon the following day and form the confused fragments of

her attacks. Once, on the day following a dream of her mother's being sick, the patient noted a bird on a post of the fence somewhere in the yard, looking at her. This she took as a sign that her mother would die. She threw a stone; the bird flew away but settled down on another side of the house. The patient then wanted to stone the bird to death. This bird also occasionally was part of her fragmented confused ideas at the onset of a seizure. The patient also stated that snakes were occasionally part of these ideas. The patient never told her mother of her dreams because she was ashamed of them and also because by this time she was having confusing sexual feelings, which were at times associated with dreams but were chiefly associated with masturbatory activities, and she felt that any talk of her fear or dreams would reveal to the parents the sexual feelings. During the psychiatric interview the patient expressed considerable fears about ever having intercourse and stated, "I'd just as soon go to bed with a snake as to sleep with a husband."

Psychologic testing showed the patient's productions on the Rorschach test to be very bizarre, and almost impossible to follow. Contact with reality appeared minimal. There were perseverating themes dealing with anatomy and landscape. The anatomic responses were mainly related to female sex anatomy. The landscape was mostly things seen in the distance, mountains with pathways leading up to them. The basis of her conflict was suggested by her response to the Mother card, on which she was severely blocked and not productive. Throughout the record many of the responses were indicative of hostility and negativism.

The Minnesota Multiphasic Personality Inventory (MMPI) showed the main elevations on the psychopathic deviate and paranoia scales, and it was stated that the profile was not easy to interpret. Many items in relation to sex, religion, and fears were filed atypically. In the sentence-completion test the patient expressed herself much of the time as confused as in the Rorschach test, sounding schizophrenic. The summary of the tests suggested that the lacunae in her functioning were probably the result of organic brain damage and there were also such severe psychologic problems that she seemed to be functioning on a psychotic level.

CASE 4.—A 36-year-old woman came to the Clinic because of epilepsy. The patient had a full-term pregnancy in 1949, toward the end of which she experienced the sudden onset of severe headaches, blindness, and convulsions. The infant was delivered by Caesarean section. The patient's eyesight gradually returned, but she was left with a left homonymous field defect. Six months after the Caesarean section the patient had a generalized convulsion and continued to have seizures from that time, about once every two months, most of them just before her menstrual period. The patient described the seizure as "starting with purple spots in the front of the left eye, and a shadow over the left eye." Then she experienced a terrific pounding temporal headache and the pounding seemed to her to say, "Kill, kill, kill." The patient then would become very light-headed, let out a cry, and become unconscious, and a generalized convulsion would follow. Specific questioning as to the nature of the mentioned shadow led to the description that this was actually a visual hallucination of the figure of an old woman. This was also in the blind field of vision.

The results of clinical neurologic examination were essentially normal. Ophthalmologic examination revealed a field defect consisting of hemianopsia in the left lower quadrant, which was attributed to a lesion involving the upper portion of the optic radiation on the right side. This was apparently the result of a cerebral infarction during the toxemia of pregnancy. The roentgenogram of the skull was normal, and the electroencephalogram revealed a delta focus in the right temporo-occipital area.

Psychiatric Data.—The patient had a severe neurosis independent of her organic disturbance, and it was felt that this was probably reinforced by the cerebral dysfunction. The patient had come from a poor, broken home and had been placed in an orphanage; she then had returned home, to a mother who was punishing and irritable. The patient's older sister never forgave the mother, but the patient repressed her rage and established a rather obsessive personality. Her marriage had not been entirely satisfactory, and she had regretted it. The pregnancy led to convulsions and the aura which was noted. She also stated to the psychiatrist that she noted in her aura ideas of "you are going to die," or "kill her" (meaning the baby daughter), and sometimes a compulsion to scream.

Results of psychologic testing on the Bender test suggested to the psychologist the possibility that the patient was quite uncomfortable in her psychosexual role. This was stated on the basis of the rather consistent manner in which the patient reproduced circles defectively, and this suggestion was borne out by the MMPI, in which the main elevation was on the MF scale. The results of the Rorschach test were quite difficult to interpret because of the patient's extreme hesitancy in giving any responses whatsoever. The responses which she did give suggested a rather disturbed emotional state.

CASE 5.—A 13-year-old girl was brought to the Clinic because of "nervous seizures." The patient had been delivered with instruments after a normal pregnancy, but was, however, "pretty roughed up." The mother was allowed to see the child only the following day. At the age of 17 months the first grand mal convulsion occurred, associated with

fever. Two years later there was again a grand mal convulsion associated with fever. During early school age the patient began to develop spells, during which she would run into the house to her mother, complaining of her stomach hurting, "a funny feeling like a tightening up" in the stomach, but with no actual pain. She would get pale and unresponsive and make gurgling noises and swallowing motions. Her eyes were staring; both hands were usually clenched or she folded them under, and there was at times some jerking. The entire episode would last a minute or more. At times the patient was also observed to mumble during the attack, but the sounds were not intelligible. After the seizure the patient usually felt tired and drowsy; there was some headache, and she was somewhat confused for a few minutes. There was no obvious aphasia following the seizure.

The child was very withdrawn, but intensive questioning led to the further memory that at the onset of her spells she would hear a noise in her ears. This was at times "sort of mumbling"; at other times she could hear somebody talking. She would recognize the voice and occasionally could understand what the voice was saying. The patient did not go into any details as to what the voices were saying, and just stated, "Oh, nothing particular."

The results of clinical neurologic examination were essentially negative. The roentgenogram of the skull was normal with the exception of some asymmetry of the face. The electroencephalogram showed a generalized dysrhythmia, which was characterized by medium-voltage activity of 5 to 7 cycles per second, and there were frequently, in addition, sharp-wave discharges in the left Sylvian area.

Psychologic Data.—A psychiatric interview was not obtained in this case, since the child was so withdrawn that it was difficult to get information from her. It was felt that possibly more information could be obtained if the patient was under the influence of amobarbital sodium (Amytal sodium). This interview was carried out during an electroencephalographic recording. In this interview the child stated that she recognized the voices during her attack as those of her mother and her aunt or her grandmother. The mother's voice would say in a rather derogatory tone, "Are you having a spell again?" At other times the voice of her aunt or her grandmother would keep repeating, "Be calm, be calm." The patient also stated during the interview that her mother was not sympathetic toward her having spells, while the aunt and the grandmother were sympathetic. The patient also made the point that the aunt and the grandmother, as well as the mother, had made such remarks to her at times but that she now heard the remarks when no one was in the room talking to her. The electroencephalographic recording showed no appreciable changes during this interview.

Case 6.—A 14½-year-old girl was brought to the Clinic because of "convulsions and spells since age 2½." At this age the patient had a high fever and a generalized convulsion. From then on, she kept having grand mal seizures about twice a year. From the age of 12½ years on, the patient's attacks included an aura of "sick feeling." She would become frightened and felt, she said, as though "a man was going to grab me." Then the patient would lose consciousness, and the mother stated that at times her head turned to the left, her eyes shifted to the left, and then a generalized grand mal seizure ensued.

The results of clinical neurologic examination were essentially normal. A roentgenogram showed the entire skull to be thicker than normal for the age, and the suture lines showed evidence of prematurely arrested growth. Arrested cerebral development was suggested. A pneumoencephalogram, which had been taken elsewhere, was reviewed at the Clinic and was regarded as normal. An electroencephalogram revealed a sharp-wave focus in the right temporal area.

Psychologic Data.—A psychiatric interview was not obtained. However, the patient related her thoughts of a man grabbing her to an incident which had occurred at the age of 7 years. As she was coming home from a store, a man called to her from a car and wanted to know if she wanted some ice cream. The patient said that he did not touch her but she was very frightened and ran to her mother.

Case 7.—A 30-year-old man came to the Clinic because of low-back pain, which was apparently due to protrusion of an intervertebral disc. As a secondary problem, he related "dizzy spells" since the age of 21 years. These occurred in groups, usually 2 to 10 a day for a period of one to three days, and then there were none for several weeks. These spells began suddenly with "a jerk, or break of the mind." It was like having "a dream," which consisted of fantasies of Indians chasing someone. All were "nonsense" and all were unpleasant; the patient dreaded them. During the spell he continued to do what he was doing, could understand people, but was unable to talk. Associated with this fantasy were a choking sensation in the throat and palpitations.

The results of clinical neurologic examination were normal with exception of the back-pain syndrome, referrable to the protrusion of the intervertebral disc. The roentgenogram of the head was normal, and the electroencephalogram showed a generalized dysrhythmia consisting of high-voltage activity of 5 to 7 cycles per second, mainly in the Sylvian areas. Occasionally discharges were seen

which were suggestive of spike-wave episodes. Further electroencephalographic studies were suggested, but the patient declined because he did not want to have his spells investigated further at that time.

Psychologic Data.—A psychiatric consultation was not obtained because of the patient's preoccupation with his back. Careful questioning led to the history, however, that fantasies of Indians had had a prominent part in this patient's life. He was raised on a farm in upper Minnesota, next to which was a swamp, and beind this swamp there were, supposedly, the Indians. He was very much frightened of this swamp and the Indians. In preschool days he was afraid of the dark and he did not want to go up to his room alone when the room was not illuminated because he "was afraid that there might be an Indian there." During grammar school he associated very closely with a boy who had been raised near an Indian reservation. This boy became his closest friend because he always told the patient stories about the life of the Indians, in occasionally rather gruesome details, which the patient now regards as having been fantasies. Also during the school age, as soon as the patient learned to read, his main interest was reading about American Indians. He now realizes that his fear of Indians was unjustified, but he still takes an active interest, visiting shows performed by Indian tribes. Detailed questioning as to the nature of the "fantasy" of Indians led to the information that this was occasionally a definite visual hallucination; at other times, however, it was only a "thought of Indians doing something."

CASE 8.—A 43-year-old student of veterinary medicine came to the Clinic in May, 1954, because of "nerves" and "pressure in my head." The patient then dated the onset of his illness to mid-April, 1954, when a sore throat and, at the same time, a pressure feeling inside the head started to develop. The patient described this as follows: "I feel like a textbook picture of a horse hydrocephalus." He was convinced that he had had sinusitis, which had done something to his brain by means of toxins going through the spinal fluid and to the brain. Other complaints included loss of interest in his studies as well as in his recreational activities, loss of appetite, nausea, shooting pains in his temples, soreness of the eyeballs, and episodes of hallucinatory experiences. These hallucinations were always abrupt in onset, lasted a few seconds, and terminated suddenly. They were accompanied by a "wave of sickness' going through his body. The patient experienced two types of visual hallucinations. The following is a verbal account as it was recorded on magnetic tape: "It was a man standing at a workbench with his back to me, and his wife was doing similar work at a nearby workbench and she made some type of error and I considered his correction of her error rather rude in the moment. Why it affected me that way, I don't know; but it did, rather rude. Either in absence of saying anything or actually scolding her, but there was a mental impression made on me that he was rather rude."

The patient experienced this hallucination twice; then it gave way to what he called "the standardized vision." He stated that this consisted of "four figures, let's say four people, up in the distance in another world or in the heavens, and there seemed to be a corresponding four figures down here on the earth that were doing some type of work of which I was observant, but as they made errors the corrections or reports from these four figures high up in the heavens, they would come down and it amazed me how these figures up here could know that they made an error, it amazed me, how this silent report came down. It rather shocked me, we'll say, the report of their error coming through my brain [here the patient giggled] reaching these poor people, and I am sorry they are being corrected or being told that they made a mistake."

The patient had never had a grand mal seizure, and consciousness had always been retained during these hallucinatory episodes.

The results of clinical neurologic examination were normal with the exception of the patient's mental state. He appeared hypomanic and loquacious, and his affect was inappropriate; for instance, he giggled while complaining of severe headaches. A roentgenogram of the head was normal. The electroencephalogram, however, revealed a delta focus in the right temporoparietal area, and perimetry suggested a left homonymous upper quadrant defect. This examination, however, was not conclusive because of the patient's strenuous objections to the test.

Ventriculography demonstrated a mass lesion in the right temporal lobe, and subsequent craniotomy led to the removal of a highly malignant astrocytoma from the anterior portion of the right temporal lobe.

Psychiatric Investigation.—The patient gave evidence of an obsessive-compulsive type of personality structure with marked feelings of inferiority. He had always been extremely perfectionistic, and he felt that people were not taking things seriously enough. For instance, he felt that even the veterinary school was not as well run as it should have been. The only statement which he volunteered in regard to his father was that he had been very strict and that "he ruled but he never helped."

COMMENT

In drawing any inferences from the foregoing reports of cases, one has to proceed with great caution, since the number of cases reported is small and the data are scanty

in some instances. It may be justifiable to point out, however, that the psychic phenomena which constituted part of these patients' seizures were not foreign to their personality set-up but seemed, on the contrary, to be closely connected with the patient's wishes (Cases 1 and 2), anxieties (Cases 6 and 7), or neurotic conflicts (Cases 3, 4, and 8).

These findings are in agreement with a case reported by Ostow,[17] in which a patient who had a paranoid psychosis, with the illusion of her ear being attacked by the physician, gave evidence during her automatism that she was protecting herself from an assault directed toward her ear. There have also been in the European literature in the past two years reports about similar observations.‡

In discussing these observations, it may be permissible to draw an analogy to seizures arising in the motor cortex. It is well recognized that Jacksonian motor seizures usually start either in the thumb or in the face, or, somewhat more rarely, in the big toe. This fact becomes understandable by studying Penfield's motor homunculus, which shows that these areas have the largest cortical representations. In extending this concept to the "commemorative cortex," as Pötzl calls the archipallial structures, it might not be altogether unreasonable to assume that factors which have a decisive influence in forming a patient's character structure may have a "larger representation" than those which are only of ancillary importance. A seizure discharge arising in these structures might then be more prone to lead to recovery of the important material, whether in the form of a memory, a fantasy, a dream, or a hallucination, than of entirely insignificant data. If this concept is correct, it might also give us a lead toward the understanding of the psychologic deterioration which is frequently observed in patients with temporal-lobe seizures. If one of the decisive factors which have led to the development of neurotic mechanisms in a patient is repeated over and over again during seizures, it may be expected that over a long period of time this may have considerable influence on this patient's psyche.

A second factor may be the postictal confusional state. This paralysis of higher psychic functions, which might, again, be likened to Todd's paralysis of the motor area, does not end abruptly but, rather, blends gradually into the "normal" preseizure state. While critical control is still under abeyance, visual and auditory sensory impressions may be falsely perceived or falsely interpreted but still be integrated as such into this patient's future behavior. This, in turn, would also lead to a psychologic deterioration.

The same phenomenon can be viewed from a psychologic standpoint. One of the principal defenses against anxiety and overwhelming stimulation is repression. The act of repression requires an intact neurologic apparatus in certain areas of the central nervous system. When this intactness is not present, repression fails, the usual defense systems crumble, disturbing unconscious material erupts, anxiety mounts, and the personality structure becomes ineffective; that is, deterioration sets in.

While the relationship between seizure manifestations and life experiences may be more apparent in the neurotic patient, it is usually less so in the psychologically normal person who is subject to the temporal-lobe type of seizures. It has been pointed out in the literature that these psychic experiences in seizures are most frequently trivial occurrences of everyday life situations. In this connection, there seem to be several instances in which Pötzl's suggestion, as cited previously, seems to have considerable validity. The olfactory aura of Case 1 and the auditory hallucinations of Case 5 may be taken as examples. It would appear, however, worth while to make some further attempts to determine how trivial some of these occurrences really are. The patient is the first one to tell us, when he is asked about the psychologic phenomena, "Oh, it's

‡ References 18 to 20.

something silly," "It's nothing serious at all," or "I can't remember." It depends then on the physician whether he is satisfied with these statements or probes further for possible clues. The following account is fairly typical of a patient's behavior in such a situation.

A 36-year-old woman gave the history that at the onset of her spells she has something like a dream but she cannot remember what it is as soon as the spell is over. In an interview, which lasted more than two hours, the following statements occurred on the part of the patient: "I really can't remember"; "It's something silly, nothing serious at all"; "It's like standing in the kitchen and doing some canning, but that isn't what it is, it's something like it"; "I'm sure it doesn't mean anything"; "It hasn't got anything to do with my husband"; "It might mean something if I'd gone out with the boys before I got married." We did not obtain any positive material in this case. However, it seems of some interest that the patient diligently pointed out what "it doesn't have to do with." The patient was then placed at a light level of hypnotic trance, and the suggestion was given her to visualize the scene of her first seizure. This brought the response "kitchen" but nothing further. An attempt was then made to get some information by word association during the trance. The command was for the patient to speak out the first word that came to her mind. The patient was blocked; repeated suggestions of "first word, first word" led finally to the statement, "There is no name." It is of interest that the investigator had not at any time used the word "name," but that this was solely the patient's concept. Nothing further could be obtained from the patient. It appears that the "dream content" is not entirely forgotten in this particular instance, but parts of it are at least preconscious.

This example demonstrates some of the difficulties encountered in obtaining psychologic data, as has been pointed out earlier. The reasons for these difficulties are several: The encountered material is regarded by the patient as foreign to his personality; it would otherwise arouse anxiety and may for this reason be repressed or, in the patient's language, "forgotten." In order to obtain these data, a long-term psychotherapeutic relationship may have to be established. Occasionally it may be of help to collect some material as soon as the witnessed seizure has ended and the patient becomes responsive before repression of the data can take place again (Case 3). This is, however, complicated by the postictal confusional state, and in some cases by aphasia. In fact, it is possible that the postictal confusional state is enhanced by the necessity of handling psychologically the threatening thoughts or impulses.

A final major difficulty is that, even if these previously mentioned problems are satisfactorily controlled, there will be a number of patients who "don't know" what the dreams or ideas may be. This was suggested by a patient who was observed in an automatism. The patient was laughing and giggling at that time, and, when asked the question "What happened?," he said, "Oh, nothing now, it happened a long time ago," and kept on laughing. In spite of insistent questioning during this phase, no information could be obtained. Five minutes later the patient had complete amnesia for the entire seizure and denied vigorously having had one in the laboratory. An amobarbital sodium interview was then carried out in an attempt to find out what had "happened a long time ago." This was entirely unsuccessful. Although the patient talked freely on all other subjects, he could not give any of the desired information. Whether the psychologic barrier in this case was such that it could not be broken even with the aid of amobarbital sodium, or whether the seizure discharges spread so rapidly that consciousness was obliterated before the content of the dreams or memory could be fully recorded, is an open question.

Notwithstanding these difficulties, however, it would appear worth while to extend the observations which were presented in this communication to a larger group of patients, for it might well be that the above-observed correlations constitute the rule rather than the exception in patients with temporal-lobe seizures. Not only may this be of theoretical interest, but eventually it might lead to a better therapeutic management of the individual patient.

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Analysis and Therapy of Cerebellar Ataxia and Asynergia

HERMAN KABAT, M.D., Ph.D., San Francisco

It has been known for many years that the cerebellum is concerned with coordination of movement, with muscle tonus, and with equilibrium. The early experimental work of Luciani [20] on ablation of the cerebellum demonstrated his famous triad, "asthenia, atonia and ataxia." Sherrington [28] called the cerebellum the "head ganglion of the proprioceptive system" and considered that it functions as a whole. Phylogenetic investigations by Bolk [6] and experimental studies by van Rijnberk [27] led to the view that there is specific localization of function within the cerebellum.

Subdivision of the cerebellum into three fundamental parts is now generally accepted.[4] The archicerebellum, or flocculonodular lobe, has primarily vestibular connections and is concerned with equilibrium. The paleocerebellum, made up of most of the anterior lobe and part of the posterior lobe, is concerned primarily with muscle tonus. The neocerebellum, which has enlarged enormously in vertebrate evolution, along with development of the cerebral cortex, is made up of the cerebellar hemispheres and is concerned with coordination of voluntary movement, particularly of the extremities.

Adrian,[1] and later Dow,[9] observed that the frequency of the electrical activity of the cerebellum is one of the highest within the entire nervous system (approximately 300 per second). This fast activity is due to intrinsic cerebellar mechanisms, since it persists several days after transection of all afferent and efferent fibers.[26] These spontaneous fast discharges are localized in the Purkinje cells or granule-basket cell complexes.

A surprising finding is the observation of Snider [25] that tactile, auditory, and visual impulses project to discrete areas of the cerebellum, in spite of the fact that the cerebellum plays no role, as far as we know, in conscious sensation. Also, motor, tactile, auditory, and visual areas in the cerebral cortex project to the corresponding cerebellar areas, which, in turn, project back on the specific cerebral areas. These pathways are in addition to the well-known strong proprioceptive connections of the cerebellum. Although conscious propioception apparently functions independently of the cerebellum, chimpanzees suffered permanent loss of a trained proprioceptive skill (weight discrimination) when both medial lemniscus and brachium conjunctivum were sectioned, but did not lose this skill permanently with section of either tract alone.[24]

It is well established that electrical stimulation of the anterior lobe of the cerebellum suppresses the extensor tone of decerebrate rigidity.[10] However, this effect is greatly modified by the position of the head in space,[17] with maximum inhibition observed in the supine position and maximum facilitation of extensor tonus from the same cerebellar stimulus in the prone position. The effect of position is abolished after bilateral destruction of the labyrinth. Furthermore, Moruzzi [22] showed that stimulation of the anterior lobe of the cerebellum can either facilitate or suppress cortically induced movements, depending on whether the motor cortex is hypoactive or hyperactive at the time. Depending on the frequency of the stimu-

lating current, the same point on the cerebellar cortex can produce either facilitation or suppression of cortically induced movement, acting through the bulbar facilitatory or suppressor areas.[25] Also, Walker [28] demonstrated a marked increase in background electrical activity of cerebral motor areas from stimulation of the cerebellar hemisphere.

Electrical stimulation of the cerebellum results in discrete movements. Hare, Magoun, and Ranson [11] stimulated the cerebellar nuclei in decerebrate cats and observed during stimulation strong flexion of the ipsilateral limbs and trunk, along with extension of the contralateral limbs. On withdrawal of the stimulus, a prolonged "rebound" posture in the opposite pattern occurred: contralateral flexion and ipsilateral extension of the extremities and contralateral concavity of the trunk. Clark [7] stimulated the cerebellar cortex in unanesthetized cats and observed movements in three phases: the phase of stimulus, the rebound, and the long aftereffect.

Delgado and Schulman [8] permanently implanted electrodes in the cerebral motor cortex and the cerebellar hemispheres and studied the responses to electrical stimulation in the awake, unrestrained cats for several months. Discrete, well-coordinated movements were elicited from threshold stimulation of the cerebellum which were almost indistinguishable from those from the cerebral motor area. With stronger stimuli to the cerebellum rebound reactions occurred. Representation of movements was diffuse, rather than discrete, in the neocerebellum. Equilibratory changes, causing falling homolateral or contralateral to the side of stimulation, were evoked by cerebellar stimulation and lasted three to five minutes after stimulation. When the cerebral motor area and the cerebellum were stimulated simultaneously, motor effects from each retained their distinctive characteristics, with coordinated interactions. Excitability of the cerebral motor area was unaffected by simultaneous stimulation of the cerebellum. Destruction of the anterior and posterior sigmoidal gyri altered neither the threshold nor the character of movements evoked from the cerebellum. Destruction of the cerebellum resulted in severe postural defects without changing the character of movements evoked from the cerebral motor area. In other words, the cerebellar hemispheres and cerebral motor cortex produce movements independently and do not particularly influence each other in the intact waking animal.

Ablation of the neocerebellar hemisphere has surprisingly little effect in cats and dogs. In monkeys, ataxia and hypotonia supervene, but the animal recovers apparently completely in about six weeks. More profound and lasting homolateral asynergia in voluntary movement, ataxia, and hypotonia result from neocerebellar ablation in chimpanzees and cerebellar lesions in man.[10] Section of the superior cerebellar peduncle produces a similar homolateral asynergia and ataxia with intention tremor.[10] On the other hand, section of the rubrospinal tract results in profound ipsilateral hypokinesis but no ataxia. Furthermore, section of the cerebellothalamic, the cerebellopallidal, or the cerebellospinal pathway does not result in ataxia if the pathway is damaged once it has left the brachium conjunctivum. Cerebellar ataxia cannot be produced by any noncerebellar lesion short of total abolition of the outflow through the brachium conjunctivum.[21]

The great bulk of the cerebellum in man is made up of the neocerebellum, which apparently has as its primary function the coordination of voluntary movement through the close relationship with the cerebral motor cortex. According to Holmes,[12] the essential disturbances are (1) postural hypotonia; (2) asthenia and fatigability of the muscles; (3) abnormalities in the rate, regularity, and force of voluntary movements, and (4) failure of certain associated movements. Some of the clinical features of the asynergia or incoordination are intention tremor, dysmetria, decomposition of movement, rebound, past pointing, adiadokokinesis, ataxia, nystagmus, and speech disturbances.

PRESENT STUDY

The present report deals with clinical observations on neuromuscular function in a large series of patients, with disease or injury of the cerebellum or its pathways, who were under an intensive rehabilitation program. Most of the patients suffered from multiple sclerosis,[13] with varying degrees of cerebellar symptomatology, but patients with familial cerebellar ataxia, brain trauma with cerebellar involvement, cerebellar atrophy, and other conditions were also studied. In addition to the usual clinical tests of cerebellar disease and functional tests, each patient had repeated careful muscle testing for both strength and endurance of the different muscle groups.

A number of techniques of proprioceptive facilitation had been developed in an attempt to accelerate recovery of neuromuscular function in patients with paralysis.[15] Among these was the technique of reversal of antagonists, applying Sherrington's principle of successive induction. One form of this method was called "rhythmic stabilization," in which the patient attempts to hold a joint rigid while the examiner applies resistance rhythmically and alternately to the antagonistic muscles in an attempt to move the joint. As an example, the patient holds the wrist rigid in the neutral position while the examiner alternately and repeatedly applies resistance to the wrist extensors and to the wrist flexors, attempting to move the wrist joint. The normal subject can perform this test precisely without rebound, carrying out voluntary isometric cocontraction of the antagonistic muscles, as well as alternately increasing the isometric contraction of the muscles to prevent the applied resistance from producing any joint motion. Patients with lesions of the corticospinal tract, paleostriatum, neostriatum, lower motor neurons, nerves, or muscles performed rhythmic stabilization precisely and well, in keeping with the degree of residual voluntary motor power. On the other hand, patients with cerebellar involvement showed rather marked deficiency in performing rhythmic stabilization.[14] Even a slight cerebellar symptomatology was correlated with significant deficiency in this test, so that rhythmic stabilization could be applied as a sensitive test of cerebellar function. The performance of rhythmic stabilization did not correlate with the voluntary power of active motion of the muscle groups but correlated closely with the degree of cerebellar asynergia.

The patient is best tested lying on a table. In general, the rhythmic stabilization test is performed in positions in which gravity is not a factor. Abduction-adduction of the hip joint is tested with the patient supine, with the heel resting lightly in the examiner's hand as he applies alternate resistance and the patient attempts to prevent horizontal motion of the joint. Knee motion is tested at 90 degrees of flexion with the subject either prone or sitting. Hip rotation can be tested in the same position. The limb is supported so that all muscles are relaxed and only the isometric cocontraction is required. The ankle joint is tested in the neutral position. Similar positions, with gravity eliminated, are used for the rhythmic stabilization test on the upper extremity. This test can also be applied for neck and trunk motions. The power of isolated voluntary motion of each antagonistic muscle group is also tested and compared with the response in the rhythmic stabilization test.

The response to the rhythmic stabilization test varies with the severity of cerebellar involvement. In the mild case, there is little or no rebound (isotonic rather than isometric contraction), and rapid, and sometimes irregular, alternation is necessary to demonstrate slight joint movement, owing to a delayed isometric response, as well as some weakness of isometric contraction. As the severity of cerebellar asynergia increases, more and more joint movement appears on testing, even with slow rhythmic alternation, greater weakness of isometric contraction, and more substitution of voluntary isotonic for isometric contraction (rebound). Also, performance of the test rapidly deteriorates as a result of fatigue, with severer cerebellar symptomatology. With very severe cerebellar disease, rhythmic stabilization cannot be performed: The joint can be moved readily through a wide range, and the patient states that he does not know how to prevent the movement; he demonstrates only isotonic contraction, with marked rebound. In such cases, testing of the isolated motions of the antagonists demonstrates isotonic contraction with rapid fatigability but little or no ability to "hold" or to perform isometric contraction voluntarily, even in a single muscle.

The rhythmic stabilization test has been of clinical value in diagnosis. In patients with mild cerebellar disease, other tests, such as the heel-to-knee test, failed to show dysmetria or intention tremor, but rhythmic stabilization was definitely deficient. This finding in several cases not only helped to explain the ataxic symptoms but also, added

to upper motor neuron signs, helped to establish a clinical diagnosis of multiple sclerosis.

Rhythmic stabilization has also been of clinical value in elucidating masked cerebellar involvement, particularly in patients with multiple sclerosis. For example, in patients with corticospinal lesions, the paralysis or spasticity may prevent the application of the usual cerebellar tests, such as the heel-to-knee test or the test for pendulousness of the leg.[20] In this situation, the rhythmic stabilization test can be readily applied to determine whether or not asynergia is also present, and to what degree. Again, the demonstration of cerebellar involvement may be of considerable value in establishing the correct diagnosis.

The deficiencies in neuromuscular function revealed by the rhythmic stabilization test appear to be basic in the understanding of asynergia. The deficiency in voluntary isometric cocontraction of antagonists and the diminution of isometric as compared with isotonic contraction, with consequent imbalance and exaggeration of isotonic contraction, may help to explain the other signs of cerebellar disease. Rebound is obviously related to the exaggerated isotonic contraction and failure of the isometric "braking" mechanism of the antagonist. Altenburger [2] found that the brake action of the antagonist is less precise (delayed) or is absent in cerebellar disease. Adiadokokinesis, intention tremor, dysmetria, and ataxia can also be readily understood on this basis. For example, the deficiency of the isometric braking mechanism and the substitution of isotonic contraction would result in irregular shifting back and forth in an attempt to reach a fixed point, or in intention tremor.

It appears to be a reasonable hypothesis that voluntary isometric contraction and isometric cocontraction of antagonists represents one of the fundamental mechanisms of coordination in voluntary movement. The neocerebellum appears to have the function of facilitating voluntary isometric contraction and cocontraction. Deficiency of this highly sensitive "feedback" mechanism for applying an isometric brake leads to ataxia and asynergia.

Unfortunately, very little is known about the neurophysiological mechanisms of voluntary isometric contraction. Isometric contraction has been investigated almost exclusively in isolated muscle or nerve-muscle preparations, in which shortening is arbitrarily and mechanically prevented, rather than voluntarily imposed. It appears likely that there are no special muscle fibers for isometric contraction in man. Also, the muscle fibers not only can contract either isotonically or isometrically under voluntary control, but can contract isometrically at any desired muscle length. How this is brought about and the role of the neocerebellum in the process remain for future investigation.

It should be pointed out that there is still considerable lack of agreement on the action of antagonistic muscles in voluntary motion. Many texts on physiology refer only to "reciprocal innervation" of antagonists, which was demonstrated by Sherrington, and which refers to inhibition of the antagonist muscle as the agonist contracts. On the other hand, there is a good deal of evidence to support the concept of cocontraction of antagonists in voluntary movement.[19]

Coordination in voluntary movement is not entirely a matter of a brake mechanism by the antagonist muscles. If this were so, asynergia should result from paralysis of the antagonist. In poliomyelitis, nerve injuries, and spinal cord transection, there may be complete paralysis of the antagonist without incoordination. For example, if the triceps is paralyzed but the biceps is not, there is no deficiency in coordination and precision of voluntary movement except in positions in which the triceps has to function against gravity. Synergy in motion of the elbow is presumably provided by the neocerebellar influence on the biceps alone.

While hypotonia has received emphasis as a factor in cerebellar asynergia,[12] it cannot be looked upon as the primary cause. The mere fact that a spastic extremity may show cerebellar signs, as is frequently the case in multiple sclerosis, shows that hypo-

tonia is not essential for asynergia. If spastic paralysis is severe, the usual cerebellar signs may be absent; but rhythmic stabilization can bring out the masked cerebellar involvement, which may be quite marked. In monkeys, Aring and Fulton [3] demonstrated diminution of intention tremor from cerebellar lesions by subsequent ablation of the contralateral Area 4, but this was probably due solely to the decrease in volitional movement.

Asthenia was recognized by Luciani [20] as a primary cerebellar symptom. This is characterized in man not so much by weakness as by rapid fatigability of the muscles.[10] This accounts, at least in part, for the marked fatigue which is such a problem in multiple sclerosis. While the patients with cerebellar lesions show a lack of endurance, there appears to be much greater fatigability of voluntary isometric than of isotonic contraction.

Routine muscle testing has demonstrated specific weakness of certain muscle groups in patients with cerebellar ataxia. For example, the toe flexors, the grasp mechanism of the foot, and, to a less extent, the plantar flexors, usually show weakness and fatigability. On the other hand, the toe extensors and ankle dorsiflexors are usually strong and do not fatigue rapidly. This specific muscle imbalance appears to be more marked the severer the ataxia. One should note that this muscle imbalance is the opposite of that frequently seen in corticospinal lesions, in which the toe extensors and ankle dorsiflexors are more affected than the toe flexors and plantar flexors, leading to foot drop.

Weakness and fatigability of the toe flexors with imbalance, as compared with the antagonists, have been used as one index of cerebellar ataxia. This has been particularly useful in patients with multiple sclerosis, who frequently show combined corticospinal and cerebellar signs in the same extremity. Many such patients have hyperactive deep reflexes and a positive Babinski sign, along with cerebellar ataxia. If the toe flexors are weak while the toe extensors and ankle dorsiflexors are strong, one may presume that the functional deficiency in voluntary motion is primarily cerebellar. If dorsiflexion is weak but toe flexion quite good, the deficiency in motor function can be considered primarily corticospinal. Or the functional deficiencies may both be present, in various degrees. This information aids in planning neuromuscular rehabilitation.

Other specific muscle imbalances observed in the lower extremity in cerebellar disease include weakness of the hamstrings, with greater power and endurance of the quadriceps; weakness of the peroneals and greater power of the tibialis anterior, and weakness of the gluteus medius and greater power of the psoas and adductors. Most of these muscle imbalances are also observed in corticospinal lesions.

The muscle imbalances are of significance in understanding the kinesiology of cerebellar ataxia. The weakness and fatigability of the toe flexors and hamstrings lead to a definite tendency toward locking of the knee and extension of the toes in balance and gait. If a normal person locks his knee and extends his toes, he has much greater difficulty in balancing on one foot. Since in the patient with cerebellar lesions these muscle imbalances are combined with deficiency in rhythmic stabilization and exaggeration of isotonic contraction, there is even greater difficulty in standing balance.

The observations on rhythmic stabilization and muscle imbalances in cerebellar disease have led to worth-while applications to neuromuscular rehabilitation. Patients with cerebellar ataxia have previously been treated with Frenkel exercises,[18] which are primarily direct coordination practice in walking or in bed. In addition to such training in coordination, we have added a number of specific therapeutic measures which have proved valuable in improving cerebellar ataxia. These include the following:

1. Resistive exercises to correct muscle imbalances, utilizing techniques of proprioceptive facilitation.
2. Resistive exercises to develop strength and endurance of voluntary isometric contraction and cocontraction.

3. Training in balance and gait, with emphasis on toe flexion and keeping the knees unlocked. This also includes resistive therapy for standing balance, with concentration on isometric contraction and elimination of rebound.

This program not only has led to decrease in the cerebellar ataxia and fatigability, but also has resulted in significant improvement in the muscle imbalances and in the response to the rhythmic stabilization test and other functional cerebellar tests.

Muscle imbalances have also been demonstrated in the upper extremity in cerebellar asynergia. Most interesting has been the greater weakness and fatigability of shoulder adduction and extension as compared with shoulder abduction and flexion. This may account for the tendency to abduction seen as a rule in cerebellar cases in the past-pointing test. Other imbalances observed were weaker external rotation than internal rotation of the shoulder; weaker triceps than biceps; weaker wrist and finger extension than wrist and finger flexion. The latter imbalances are similar to those seen with corticospinal lesions. Neuromuscular reeducation for correction of muscle imbalances, and for voluntary isometric contraction and cocontraction and endurance, in addition to occupational therapy, has been of value in reducing cerebellar asynergia in the upper extremity.

It is interesting to speculate on the relationship between the corpus striatum and the cerebellum. These two large regulatory structures in the motor system may be antagonistic in function with an equilibrium between them, perhaps, as the normal state. It has been pointed out that the cerebellum apparently facilitates voluntary isometric contraction. Deficiency of cerebellar function results in relative exaggeration of isotonic contraction and diminished isometric contraction, producing ataxia and asynergia, as well as hypotonia. There is also asthenia, particularly rapid fatigability of voluntary isometric contraction. On the other hand, lesions of the paleostriatum, resulting in Parkinson's disease, are associated, aside from the resting tremor, with deficiency in voluntary isotonic contraction, with relative exaggeration of isometric contraction.[16] There are difficulty in initiating isotonic contraction, weakness, slowness, and fatigability of active voluntary movement. Isometric contraction is carried out much more strongly, and rhythmic stabilization is performed effectively. While a patient with cerebellar disease may have no difficulty in raising his arm, he fatigues rapidly in attempting to hold it up against resistance. In contrast, the patient with Parkinson's disease may find it quite difficult to raise his arm, but he can hold it up much longer against resistance without fatigue. In contrast to the hypotonia of cerebellar involvement, lesions of the paleostriatum result in rigidity. According to Wartenberg,[29] pendulousness of the legs is increased in cerebellar disease and decreased in Parkinson's disease.

In an interesting paper on "cerebellopallidal anisosthenia," Bing [5] points out some of the opposing effects of lesions of the two areas. He contrasts the megalographia of cerebellar disease with the micrographia of Parkinson's disease. He states that in unilateral disease the cerebellar patient underestimates weight in the affected hand, while the Parkinson's case overestimates weight on the affected side. Involuntary changes in position in the horizontal outstretched arms of the patient with eyes closed are characterized by marked and constant upward and outward movement in cerebellar disease, in contrast to the outspoken downward and inward movement of the arm in Parkinson's disease. It was pointed out earlier that patients with cerebellar asynergia show muscle imbalance with greater weakness of shoulder adductors and extensors than of their antagonists. The opposite muscle imbalance may be present in paleostriatal lesions.

One may speculate that, while voluntary motion is initiated at the motor cortex, two great regulatory mechanisms antagonistic to one another greatly influence and control the voluntary movement: The neocerebellum facilitates voluntary isometric contraction, while the paleostriatum facilitates vol-

untary isotonic contraction. Homeostatic equilibrium of these antagonistic "feedback" mechanisms leads to skilled coordinated volitional movement. While this hypothesis may be an oversimplification and is based primarily on clinical studies, it may be useful in leading to fruitful investigation of the important role of isometric and isotonic muscular contraction in voluntary motion.

SUMMARY

The rhythmic stabilization test has been developed as a useful clinical test of cerebellar asynergia.

The neocerebellum apparently has as its basic function facilitation of voluntary isometric contraction and cocontraction. Deficiency of this function leads to ataxia and asynergia.

Specific imbalances of antagonistic muscles can be demonstrated in cerebellar ataxia, particularly deficiency of the grasp mechanism of the foot, which are significant in understanding the kinesiology of the ataxia.

Specific imbalances of antagonistic muscles are also observed in cerebellar asynergia in the upper extremity. Of interest is the imbalance with weakness of shoulder adduction, which correlates with the abduction of the shoulder observed in the past-pointing test.

A program of neuromuscular reeducation based upon training of voluntary isometric contraction and cocontraction, correction of muscle imbalances of antagonists, and development of endurance has been of value in rehabilitation of patients with cerebellar ataxia and asynergia.

Opposing functions of the neocerebellum and the paleostriatum are discussed.

450 Sutter St.

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Psychological Changes Associated with Giant Pituitary Neoplasms

JAMES C. WHITE, M.D.
and
STANLEY COBB, M.D., Boston

Although nearly 600 articles concerning pituitary adenomas and craniopharyngiomas have been listed in the Quarterly Cumulative Index Medicus since its first volume, in 1916, only 13 are primarily concerned with the psychological changes which these lesions may produce if they expand upward to an unusual size. We have been able to find incidental brief allusions to this complication in a few others. Harvey Cushing [1] barely mentioned the possibility in his series of 360 pituitary adenomas; but, in a subsequent follow-up of these patients, Henderson [2] found 51 who suffered from mental deterioration, hallucinations, or somnolence in the later stages of the disease. Olivecrona, of Stockholm, who has had the most extensive modern experience with this condition, and Bakay,[3] who has reviewed his material, mention mental symptoms in only a single patient with a recurrent tumor. According to Bakay (personal communciation), this patient is now severely deteriorated in a psychiatric hospital in New York. As Jefferson [4] pointed out:

> Cushing himself was always most interested in the cases which gave the best results. . . . Other writers have, quite naturally, followed his lead. But to do so leaves the history but half told.

Despite this apparent lack of interest in the psychological complications of suprasellar expanding lesions, it is not at all surprising that large craniopharyngiomas or adenomas (usually the chromophobe variety), when they expand upward into the third ventricle, forward between the frontal lobes, or laterally into a temporal lobe, should produce changes in personality, memory, behavior, and level of consciousness, as well as seizures and disorders of autonomic control. These may be due to local compression of these important areas, or the result of diffuse pressure secondary to hydrocephalus. Jefferson has given us a clear understanding of the pathways of extension of these tumors when they grow beyond the confines of the sella turcica. Escape may then be forward between the frontal lobes, in the case of a postfixed chiasm; directly upward and backward behind the chiasm into the third ventricle, or, more rarely, in a lateral direction into a temporal lobe. The frequency with which colloid cysts of the third ventricle produce psychological disturbances has been observed by some of the authors who have written about these lesions (Poppen, Reyes, and Horrax [5]; Cairns and Mosberg [6]).

As stated above, we have been able to find only 13 indexed articles which are primarily concerned with the psychological phenomena that may arise when hypophyseal adenomas and craniopharyngiomas expand far above the confines of the diaphragma sellae. For the sake of brevity 11 of these, to which we have had access, are summarized in Table 1; the 2 not included, reported by Nobile and d'Agata [18] and Gertsberg,[19] were written in Italian and Russian. No copies of these journals are available. Meumann,[11] along with his description of two cases summarized in the Table, gives a number of early references, as far back as 1889. The paper by

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TABLE 1.—*Articles Listed in* Quarterly Cumulative Index Medicus *That Are Primarily Concerned with Psychological Phenomena Associated with Pituitary Neoplasms*

		No. of Cases	Sex; Age; Type of Psychosis	Size of Tumor: Operation or Autopsy	Comments
1	Sainton and Péron, 1923 [7]	1	M; 38; severe headaches, R. hemiparesis, loss of memory, apathy, mental deterioration, & progressive vegetative state	Autopsy: 3.5 cm. upward extension of mixed adenoma without hydrocephalus	Photograph of tumor compressing 3d ventricle, thalamus, & internal capsule on left
2	Cuel, 1924 [8]	1	F; 57; profound mental deterioration with loss of memory & progressive coma	Adenoma extended up into 3d & left ventricle	Death from hyperthermia
3	André-Thomas, 1929 [9]	1	M; 18; panhypopituitarism; apathy & mental deficiency	No verification of tumor by operation or autopsy	X-ray showed complete destruction of sella
4	Vincent and associates, 1931 [10]	1	F; 33; bilateral optic atrophy & headache; disorientation, failing memory, & progressive mental deterioration	Extensive removal of adenoma with suprasellar extension	Striking psychological improvement
5	Meumann, 1932 [11]	2	Paranoid dementia with hallucinations after onset of blindness in each	Autopsy: tumor size of "pigeon's egg" in one case; no clue to extent of growth in other	Acromegaly with characteristic bony changes & optic atrophy in both
6	Kaess, 1935 [12]	1	M; 45; with panhypopituitarism developing at 15; epilepsy, apathy, somnolence, & hallucinations	Craniopharyngioma diagnosed by enlargement of sella & calcification	Still alive at time of report, but somnolent and deteriorated
7	Weinberger & Grant, 1940 [13]	16	Visual hallucinations associated with pituitary adenomas & cysts with partial or complete loss of vision; no other psychological abnormalities	Tumors all compressed optic nerves or chiasm, but majority did not have suprasellar expansion	Authors conclude that visual hallucinations may arise from any portion of visual pathway
8	Wagner, 1942 [14]	3	Craniopharyngiomas with autonomic & psychotic manifestations: Korsakoff syndrome, euphoria, apathy, somnolence, & coma	Large suprasellar cysts seen post mortem	Excellent photographs showing size of tumors
9	David & Hécaen, 1942 [15]	1	F; 38; hallucinations consisting of elaborate formed images	Adenoma removed, including portion compressing 3d ventricle	Authors state that these attacks were intermediary states between phenomenon of déjà vu & hallucinations of memory
10	Langford & Klingman, 1942 [16]	1	10-yr.-old child; emotionally unbalanced, restless, irritable, & daydreaming	Drainage of large suprasellar cyst	Great improvement in behavior
11	Obrador and others, 1951 [17]	1	Acromegaly with postoperative recurrence of tumor; complete memory loss, confusion, and disorientation; no increase in intracranial pressure	Autopsy: walls of 3d ventricle compressed by tumor	Photographs illustrating extent & position of tumor

Sainton and Péron [7] also cites some other early accounts, dating back to Schuster's book, published in 1902.[20] Schuster stated that the pituitary tumors give rise to psychiatric changes in a larger proportion of cases than any others except those invading the corpus callosum or compressing the frontal lobes.

The following additional references, not picked up in the Quarterly Cumulative Index because their titles failed to mention psychological complications, are of particular interest in this connection: Frazier,[21] in reviewing what he called his hypophyseal stalk tumors, mentioned "symptoms of extraneous origin not related to either the hypophysis, the discs, or the fields." In this category he included signs of frontal lobe invasion, such as defective memory, psychosis, delusions, jocularity, irritability, viciousness, mental apathy, and depression. It is evident, as we shall show below, that he was combining symptoms produced by hypothalmic invasion with those of pressure on the frontal lobes. In discussing his suprasellar adenomas, he makes no mention of mental changes.

Other papers which report individual cases with amnesic states produced by deep midline lesions in the region of the third ventricle were written by Foerster and Gagel [22]; Lhermitte, Doussinet, and de Ajuriaguerra [23]; Benedek and Juba [24]; Conrad and Ule,[25] and Sprofkin and Sciarra.[26] In the case of Foerster and Gagel's patient with a craniopharyngioma the mental symptoms cleared when the cyst was drained and a portion of its wall removed.

Jefferson,[4] in his paper on giant extensions of chromophobe adenomas, described two patients with hypothalmic involvement. These had severe headaches, polyuria, obesity, and fluctuations in body temperature. Mental changes consisted of increasing irritability, lethargy, and somnolence. Both died with hyperpyrexia after operation. In his experience with four cases of extension forward between the frontal lobes, epilepsy was a complication in two, together with irritability, deterioration of character, and apathy. Two patients with lateral expansion of the tumor into a temporal lobe had uncinate fits, emotional instability, and other psychological changes.

Love and Marshall,[27] in a review of 100 craniopharyngiomas from the Mayo Clinic, noted "psychiatric changes which could be attributed to hypothalmic involvement . . . in four cases. In each instance the behavior was in the form of a manic state. Impairment of memory, confusion, defective judgment or retarded cerebration was noted in 15 additional cases, but probably could be attributed to involvement of the frontal lobes." As they pointed out, "It is difficult to distinguish clinically between the psychiatric changes which occur with involvement of the frontal lobes and those which sometimes accompany hypothalmic damage."

Trumble,[28] in his discussion of 13 patients with large chromophobe adenomas, states:

> In those cases in which there was severe pressure upon and deformity of the hypothalamus . . . drowsiness was usually a well-marked feature, but the value of this symptom . . . is somewhat diminished because it was present in other cases in which the hypothalamus did not appear to be seriously disturbed. Changes in personality and dulling of mentality were usually present when there was a massive intracranial extension in any situation. In such cases it may be difficult to decide whether the changes are due to interference with the functions of the hypothalamus or frontal lobes, or to the development of hydrocephalus.

Williams and Pennybacker [29] described a series of 21 patients with large craniopharyngiomas which extended upward into this territory. Fifteen showed severe to moderate disturbances in memory. This did not depend on any increase in intracranial pressure from hydrocephalus, and the patients generally maintained a good personality and intellect. These authors describe in detail four examples of large cystic tumors in the hypothalamic area and the striking mental changes, resembling Korsakoff's syndrome, that were produced. Not only was there a profound loss of recent memory, but these patients tended to confabulate and had hallucinations. They were disoriented as to time and place and were often drowsy. When the

cysts were drained, there was an improvement in the mental picture.

To call further attention to the importance of psychological disturbances, which usually indicate a giant, inoperable lesion, we can add five examples. All but one of these patients have undergone extensive psychiatric investigation. For the sake of brevity we have omitted endocrinological details and all but the more important neurological and other findings which are of interest in connection with the size and position of the extrasellar extensions.

REPORT OF CASES

Case 1.—W. J., a 46-year-old retired chief gunner's mate, was operated upon by one of us in 1944 at the U. S. Naval Hospital at Chelsea, Mass. This case history has already been published by White and Warren [30] because of the unusual size and extension of the chromophobe adenoma. Despite a partial removal of the right frontal pole, it was impossible to resect more than a small portion of this enormous growth, which filled a large part of the anterior fossa and compressed the temporal tip, as well as both frontal lobes. The patient died without recovering consciousness.

This patient had a long history, dating back to 1935, when vision began to fail in the right eye. He was retired from active service because of constricting temporal fields and early optic atrophy. He had continued to live in China. After returning to this country, in 1941, he boarded with his mother. She noticed an increasing change in his personality. He was reluctant to leave the house, partly because of his poor vision, but also because he had lost all ambition and wanted only to sit in his room and listen to the radio. His mother, who claimed he had always been "a good boy," was distressed because he had become so irritable and profane. He was admitted to the Naval Hospital on April 9, 1944, because of three epileptic seizures during the preceding night. After the third he remained in coma and six hours later was admitted in postictal stupor. This gradually cleared, and he then had no further fits, on anticonvulsant medication. He was belligerent and profane, lacked initiative, and showed poor judgment.

Examination showed the characteristic changes of mild hypopituitarism. His vision was reduced to counting fingers at 1 ft. in O. D. and 20/40 in O. S. There was moderate atrophy of the nerve heads, but no papilledema. The temporal field of vision was completely lost in each eye, the pupils reacting only when the light was directed against the temporal half of each retina. For some unexplained reason, sense of smell was preserved in each nostril. Other cranial nerves were unaffected, and there were no other neurological abnormalities.

X-rays of the skull disclosed a very large expanding intrasellar tumor, with thinning and upward tipping of the anterior clinoid processes, and erosion and backward displacement of the posterior processes. In addition, there was destruction of the dorsum and floor of the sella turcica with erosion into the sphenoid sinus. The pineal body was displaced somewhat posteriorly.

Lumbar puncture revealed that pressure was 120 mm. and the protein elevated to 53 mg. per 100 cc. Realizing the enormous size of the neoplasm from both the objective changes and psychological disturbances, which resembled a postlobotomy state, we undertook operation as a rather desperate measure because of the danger of recurrent severe seizures. Through a right transfrontal craniotomy, after elevation of the frontal lobe, an enormous tumor could be seen filling the anterior fossa forward to the crista galli. A large portion of the frontal pole was removed and tumor scalloped out to clear the olfactory groove and decompress the right optic nerve, but it proved impossible to expose the optic nerve on the left or the chiasm. The tumor could be seen extending far laterally along the sphenoid ridge and across under the frontal lobe on the left, as well as upward between the hemispheres. At this time the blood pressure fell to 50 mm., although blood loss had not appeared to be excessive and had been adequately replaced. The incision was therefore closed. His blood pressure then rose to normal, but fell again 18 hours later, with progressive failure in vital signs and rapid death.

Autopsy, performed by Dr. Shields Warren, disclosed a well-demarcated chromophobe adenoma arising from the floor of the anterior fossa and enlarged sella turcica (Fig. 1). Its upper surface presented on the floor of the right lateral ventricle and over a portion of the third ventricle. The left lateral ventricle was compressed from below, but not invaded. The hypothalamus was displaced upward and backward, together with the basal ganglia on the left side. The tumor, made up predominantly of chromophobe cells, showed no evidence of malignant change, although it had invaded the right lateral ventricle and optic chiasm. It extended from the crista galli to the pons, a distance of 12 cm., upward 5.3 cm. above the floor of the anterior fossa, and reached a maximum width of 7 cm.

Case 2.—Mrs. A. F., a 43-year-old housewife, was first admitted on the neurological service in March, 1950, because of progressive visual failure. Eye examination showed bitemporal hemianopsia with optic atrophy. She had, in addition, amenorrhea, lactorrhea, and obesity. Skull films showed

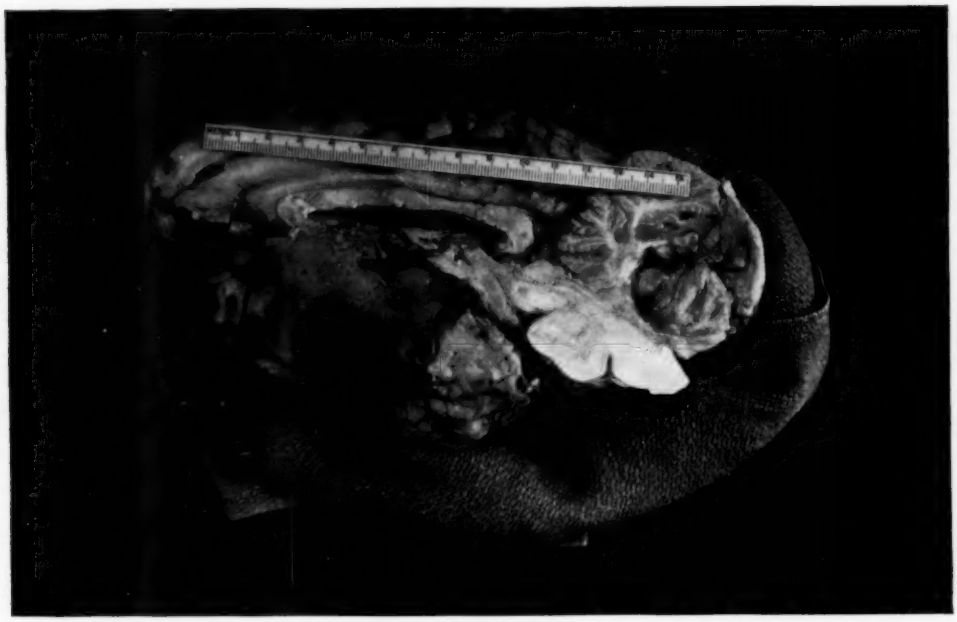


Fig. 1 (Case 1).—Midsagittal section of brain at autopsy. Reproduced from White, J. C., and Warren, S.: J. Neurosurg. **2**:126-139, 1945, with permission of the authors and Charles C Thomas, Publisher, Springfield, Ill.

wide ballooning of the sella with thinning and displacement of the clinoid processes. Had she been referred to neurosurgery, she would have had air studies to outline the extent of suprasellar extension of her adenoma, as described by Bakan and White.[31] This simple test would doubtless have indicated the need for immediate operation, at a time when the suprasellar extension could have been safely removed. Instead, she was given a 3500 r dose of x-radiation and discharged to her home, in the western part of Massachusetts.

There was at first an improvement in her eyesight and fields of vision to the point where she could read all but the finest print in the newspaper, but she failed to return to the hospital for 16 months. While lactation did not recur, she had developed headaches and recent progressive visual failure. At reexamination in May, 1952, the left eye was found to be nearly blind, and on the right visual acuity was reduced to 10/200, with loss of the temporal fields. Aside from endocrine changes consistent with mild hypopituitarism, the general neurological examination and her mental reactions at this time were not abnormal. A pneumoencephalogram with a small quantity of air now showed a 3 cm. upward extension of the tumor from the expanding sella (Fig. 2*A*).

A left transfrontal craniotomy (this patient was left-handed) was carried out on June 3, 1952, with evacuation of a 10 cc. cyst through a wide opening in its vascular capsule, freeing the compressed left optic nerve. Postoperative recovery was rapid, and the patient was discharged in 10 days with a promising recovery of vision. The histological report was chromophobe adenoma.

Two months later she was again able to read the newpaper with 15/20 vision in O. D. and recovery of the temporal half of macular vision. The left eye remained blind save for light perception. This improvement, unfortunately, was short-lived, and in November, 1952, she was again admitted, with reduction in vision to the point where she could barely count fingers. A second pneumoencephalogram showed the tumor to be larger than before and expanding into the anterior portion of the third ventricle. The dural clips placed around the opening in the cyst had been displaced upward. On Nov. 23, the large cyst was again opened and evacuated, with removal of most of its anterior capsule above the diaphragma sellae. Exposure was facilitated by cutting the left optic nerve, which was stretched to a mere thread. The cyst extended to the base of the sella without visible solid tumor.

Again, she made a smooth recovery, with return of nearly normal vision in O. D. An x-ray now showed the clips placed in the cut edges of the cyst to be collapsed nearly to the level of the clinoid processes. After another course of radiation she was sent home.

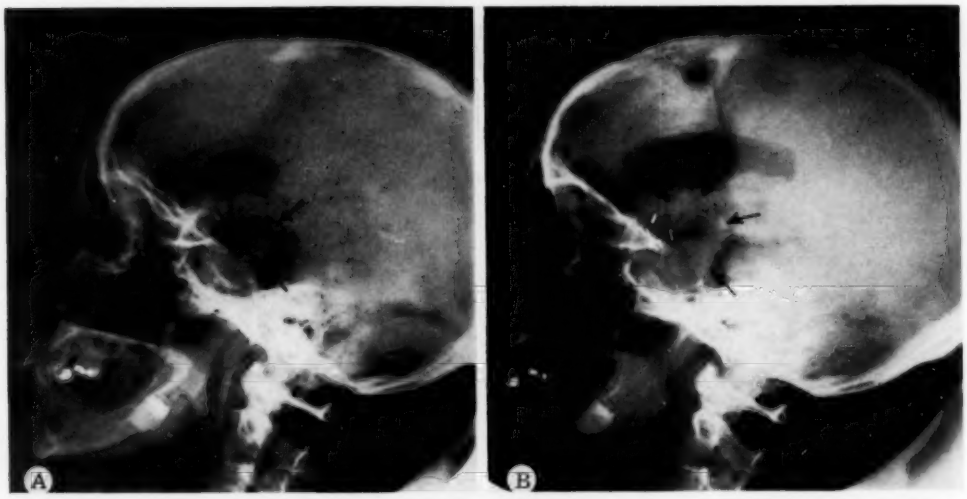


Fig. 2 (Case 2).—Pneumonencephalograms: *A*, prior to first operation (May, 1952); *B*, 10 months later (12 months before her death), before psychological deterioration was advanced.

This improvement, however, was again of short duration. Within six weeks visual acuity had fallen from 15/20 to 20/200 in O. D. To find out the present extent of the neoplasm, another pneumoencephalogram was carried out on March 21, 1953. This showed a huge upward extension of the growth, which now filled the anterior portion of the third ventricle, and beginning hydrocephalus (Fig. *2B*). Because of this rapid recurrence a transnasal drainage of the cyst was carried out by Dr. Oscar Hirsch on March 24, 1953, after which vision in O. D. again recovered to 15/30.

Nine months later vision was 15/15 in the nasal field of O. D., but mental changes were now beginning to appear. Her husband and friends reported that she was becoming drowsy and confused. She would go to sleep ironing or cooking, and it was difficult to get her out of bed till noon. Her appetite had become voracious. In addition, her memory was beginning to fail. She reported dreams and fictitious events. On one accasion she complained that there was a live rabbit in her oven. She was readmitted for psychiatric examination.

The husband reported that for over two months he had noticed deterioration of behavior, from an ambitious, conscientious housewife to a slothful and slovenly woman who was somnolent and inert, and, when aroused, showed poor judgment and fabricated childish stories. Before she became so inert, she had gone shopping and brought home many things she did not need and could not afford.

On mental examination (Jan. 8, 1954), the patient lay in bed with closed eyes. When she was aroused, her attention could be held to answer questions. She was oriented for place and person but got the date wrong by a month. She talked easily and showed some lack of inhibition, but her cheerfulness was rather flat. There were no overt delusions or hallucinations. She was unable to grasp complex problems, such as similarities. She had some insight into the fact that she was mentally disturbed, made up stories, and had a poor memory. But this did not seem to worry her. She could not retain a name for five minutes. Her ability to repeat digits was limited to five forward and two backward. On subtracting 7's from 100, she got 93, 86, and then forgot what she was trying to do. She showed some distractability.

In summary, the patient was apathetic, somnolent, and obtuse; when aroused, cheerful and distractable. She showed gross defects of attention and memory with confabulation.

A second transnasal drainage through the base of this cyst was then performed by Dr. Hirsch on Jan. 15, 1954, but only a small amount of broken-down tissue was obtained. She remained very disoriented, not knowing where she was, how long she had been hospitalized, or even that she had been operated upon. On one occasion she thought she was on her farm and the side of her bed was part of an animal's stall. Although there was no aphasia or perceptual difficulty, she could not remember even the age of her son or husband, or what had occurred a few minutes before. She confabulated constantly.

Neurological examination, by Dr. Raymond D. Adams on Jan. 19, 1954, showed her to be worse. She took no interest in anything, showed no emotion, and answered after long pauses, sometimes incoherently. Orientation for time and place was poor; memory for names of objects was less than three minutes. Her speech was well articulated and

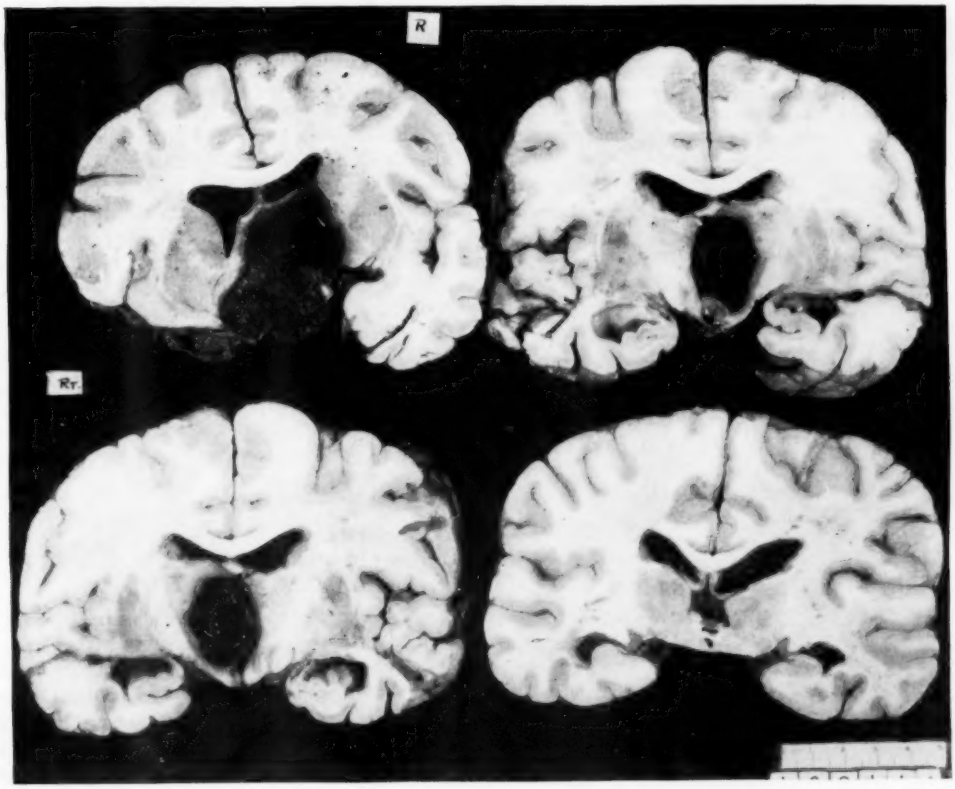
used in correct context. Dr. Adams compared the picture to that of Korsakoff's psychosis and related it to disease of the diencephalon.

The psychologist's test on Jan. 29, 1954, was reported as follows: "Digit span has improved since a week ago: five forward and two backward, as compared with four forward and none backward. She now knows her full name and gives her age, but she is still disoriented for time and place. She succeeds in counting backward and reciting the alphabet. She does not retain a news story, nor does she recall content on suggestion. She confabulates freely when pressed for a response. Attention and directional activity are improved—she is now able to attempt to draw designs, though she fails to remember them and cannot draw them even with repeated presentation. Also, she makes a more sustained effort in drawing, succeeding in making a head, neck, and shoulders when asked to draw a man. Previously, a week earlier, that is, she had made a haphazard drawing, which she then called a bird and which she affirmed she had been instructed to draw. She retains a few easy word associations, but by the third run-off of the series she had forgotten them. Recognition of missing picture detail is poor, with confabulation, perseveration, and poor perception of content. Comprehension is variable, with characteristically limited output of integrative energy in applying past experience and knowledge. Formulation of concepts (similarities) is also variable, and occasional good responses suggest some retention of abstractive approach."

With intraventricular pressure mounting to 200 mm., a Nosik ventriculomastoidectomy was done on Feb. 10, as the simplest procedure to enable the ventricular fluid to by-pass the obstructed third ventricle. Despite free drainage via the Eustachian tube, cerebrospinal fluid pressure continued slightly elevated, and the patient became increasingly stuporous. She was discharged to a nursing home, where she remained somnolent and died a month after operation.

The brain was obtained by sending out one of our residents to perform an autopsy. The tube leading from the temporal horn of the ventricle to the mastoid had been functioning well, and the size of

Fig. 3 (Case 2).—Postmortem coronal sections of brain.
The chromophobe adenoma has invaded the entire third ventricle. Hydrocephalus had receded after the Nosik ventriculomastoidostomy was performed, one month before her death.



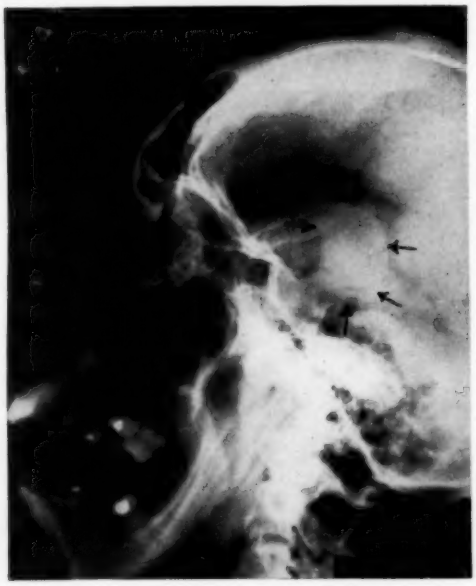
the formerly dilated lateral ventricles had decreased considerably. When the frontal lobes were elevated in removing the brain, there was a gush of brownish fluid from the ruptured capsule, leaving a large, partly solid tumor in the base of the brain. This completely filled the third ventricle from front to back and severely compressed the basal ganglia, especially on the right side (Fig. 3).

CASE 3.—Mrs. I. B., a 52-year-old housewife, had been developing clear-cut signs of acromegaly for the past 15 years. Unfortunately, the ophthalmologist whom she consulted had continued to treat her coexistent glaucoma until all useful vision was lost. The lower nasal quadrants had been preserved to the last, as is characteristic of tumors expanding upward beneath the chiasm and optic nerves. On admission, in October, 1953, she was the picture of acromegaly, with large nose, hands, feet, and sinuses, as well as splanchnomegaly and diabetes mellitus. In the films of her skull the sella turcica was greatly elongated, with flattened clinoid processes.

There was a history of a six-month "nervous breakdown" at 24, and she had been depressed in recent years. The record mentions "personality changes" but, unfortunately, does not describe them. On the ward she was drowsy by day and tended to sleep poorly and restlessly at night. She was slow, was mentally deteriorated, and showed distinct paranoid trends. Her orientation was good.

Fig. 4 (Case 3).—Pneumoencephalogram.

Arrows indicate upward expansion of adenoma, which fills the anterior portion of the third ventricle. Cranial abnormalities characteristic of acromegaly are seen in the huge frontal sinus and changes in the jaws and teeth.



On account of the alteration in her personality, we at once suspected that she would be found to have an unusually large suprasellar tumor. Lumbar pressure was not recorded, but the protein content of the cerebrospinal fluid was elevated to 85 mg. per 100 cc. The extent of the suprasellar growth was brought out by the injection of a small volume of air and posturing her head to fill the basilar cisterns and the third ventricle (Fig. 4).

Feeling that only a small portion of the growth could be removed by an intracranial approach and that the risk of mortality was prohibitive, we asked Dr. Hirsch to explore transnasally in the hope that the growth might be partly cystic and that some collapse could thus be obtained with relative safety. This was done on Nov. 4, 1953, with removal of about 10 cc. of broken-down tissue and fluid, leaving a cavity in the sella. Unfortunately, there was no recovery of vision, but a transitory amelioration of her headaches. Examination of the tissue removed indicated that this was a chromophile adenoma, in which the eosinophilic staining cells were no longer secreting actively.

After discharge her headache soon recurred and her dim vision worsened to almost total loss of light perception. Her husband thought that her personality was even more abnormal. A second transnasal evacuation of the sella was carried out on Dec. 21, 1953, but little more tumor and no fluid could be obtained. During the next three months, however, there was distinct improvement, and during the year and a half since the last operation she has held this and gradually improved more. Follow-up examination on May 27, 1955, showed that she has become less irritable, her poor memory has improved a great deal, and she has little difficulty in concentration when aroused. She fatigues easily and is dull, and even somnolent, at times. Occasionally she is restless and irritable, and rarely has acted in a belligerent manner. There are no periods of confusion except when she is awakening from sleep; at such times she is not sure whether her dreams are real or not.

CASE 4.—J. H., a 60-year-old Negro, had been in good health until four years prior to admission, when he began to notice progressive visual dimness. Several doctors told him that this could not be corrected by glasses, but he had not been referred previously to a hospital.

Visual examination on admission, in December, 1953, showed that he could only count fingers at 2 ft. (60 cm.), and this only in the upper nasal quadrant of each eye. There was bilateral optic atrophy. In addition, olfactory acuity was reduced in the left nostril. The patient showed the stigmata of mild hypopituitarism. The spinal fluid pressure

was 110 mm.; protein, 76 mg. per 100 cc. Skull films disclosed destruction of the dorsum sellae and floor of the sella turcica, together with part of the left anterior clinoid process and greater wing of the sphenoid laterally, leading the radiologists to suggest a tumor larger than the ordinary pituitary adenoma. A pneumoencephalogram disclosed a filling defect indenting the frontal poles bilaterally, greater on the left than on the right, as well as a defect in the anterior portion of the third ventricle. The aqueduct was clearly seen and was not displaced . The fourth ventricle was normal. This finding was consistent with a large, solid mass of tumor involving the sella turcica and suprasellar area.

It soon became noticeable that the patient was mentally abnormal. He accused the nurses of trying to infect him with tuberculosis, of moving him to another ward because of his race, and of lying to him, and he manifested other paranoid traits. During his cortical function test he became resistant and suspicious. His mental ability was at a dull-normal level; memory seemed normal.

On Dec. 21, 1953, a right transfrontal exploration was carried out by Dr. Louis Bakay. The chiasm was found to be pushed backward by a massive adenoma expanding upward beneath both optic nerves. When its capsule was opened, soft tumor tissue could be sucked away until pressure on the optic nerves was relieved, although the chiasm was still "fixed backward." The tumor proved to be a chromophobe adenoma.

The postoperative course was complicated by a prolonged period of hyponatremia, which responded poorly to salt replacement despite medication with cortisone and corticotropin. After 10 days he began to have delusions. He became combative and struggled with the nurses when they tried to feed or care for him. The question was raised whether this state could be due in part to a reaction to cortisone or to his electrolyte disturbance. Cortisone was therefore stopped, but without any improvement in his mental state. In addition to his disorientation and inability to concentrate, he now began to have hallucinations. Dr. Bruce Sloane, on the psychiatric service, who saw the patient at frequent intervals throughout his illness, at first regarded his peculiar behavior as evidence of a postoperative confusional state. By the end of a month, however, both he and Dr. Marc Moldawer (Dr. Fuller Albright's associate) felt that endocrine abnormalities could not be held responsible and that the patient's combativeness, refusal to eat, delusions, and increasing somnolence must be due to a "profound disturbance at the base of the brain."

During the second month the patient was given a course of radiation. Under great difficulties in holding his head in position, a dose of 2850 r was finally delivered. Nevertheless, he remained so disoriented and difficult to handle, with increasing impairment in memory and judgment, that he was finally committed to the Northampton State Hospital, two and a half months after his operation. There he was placed in restraint because he was disturbed and had to be prevented from pulling out the inlying catheter. He was in poor contact, appeared agitated, and complained that he had a "24-lb. iron shoe on his leg." He appeared to be answering questions of an hallucinatory nature, and he said that he was being persecuted by some colored people. He answered questions in broken sentences that were rather incoherent. On March 18 the auditory hallucinations seemed to be more marked and were of a persecutory nature. He remained in bed most of the time. On March 25 he appeared to be dizzy when sitting up in a chair and was more confused, stubborn, and negativistic. On April 5 cardiac decompensation seemed to be developing, and on the following day he died, with cardiac failure the apparent cause of death. It was impossible to obtain permission for autopsy.

While the patients in the four preceding cases all had adenomas (three chromophobe, one chromophile), the following, and last, case is one of craniopharyngioma.

CASE 5.—C. K., aged 46, had complained of generalized headaches for two years. For three months he had noticed difficulty in reading and a tendency to bump into people approaching on his right side. His early development had been normal with the exception of sparse pubic and axillary hair and a need to shave only twice a week. He had married at 25 and sired three children, although his libido was always low and had been absent for the past three years.

On admission, in July, 1953, the patient, an obese, graying man, showed delicate skin, fine hair, small testes, and other characteristics of panhypopituitarism. The fundi were normal, but visual acuity was reduced to 10/20 in each eye and there was a large paracentral field defect in O. D., which permitted only central vision. This soon increased to a typical bitemporal hemianopsia. Skull x-rays demonstrated erosion of both anterior clinoid processes and an enlarged sella with eroded floor. Pneumoencephalogram showed a mass under the floor of the third ventricle, lifting it up and displacing it slightly backward.

Serum electrolyte determination showed the sodium reduced to 128 mEq. At Dr. Moldawer's suggestion, he was given cortisone prior to operation. This was carried out on Nov. 4, 1953, by Dr. William H. Sweet, who opened the cyst widely beneath the optic chiasm, releasing a large amount of brownish fluid. Postoperatively the fluid intake and urine output rose to nearly 5000 cc., reverting to normal volumes after a week. Although the

serum sodium fell no lower, it could not be restored to normal by cortisone or a high salt intake.

As a second pneumonencephalogram, taken six weeks later, showed that the floor of the third ventricle was still elevated by a massive underlying lesion, Dr. Sweet reexplored on Dec. 17. This time, 12 cc. of fluid was again evacuated from the cyst and solid tumor was removed from under the left optic nerve by chipping away the tuberculum sellae. Again, there were polydipsia and polyuria (4500 cc. output daily) for the first few days. On the third day the patient suddenly developed a shock-like picture, with blood pressure and pulse unobtainable in the arms and a cardiac rate of 120 at the apex. He was stuporous, with cold, clammy, cyanosed extremities. Adrenocortical insufficiency was diagnosed and treated by intravenous hydrocortisone and corticotropin. Although no electrolyte levels were obtained at that time, the sodium level had been 145 mg. per 100 cc. the day after operation and later determinations were normal. With this treatment he recovered rapidly and soon became stable, without need for further medication.

Despite his good physical condition, the patient remained apathetic. He talked slowly. He complained of his poor vision, which had failed to improve, but without any emotional concern. His predominant mood was one of apathy rather than of depression. Cortical function tests showed impaired memory with poor abstract thinking and learning ability and difficulty in concentrating. When seen in May, 1954, he was almost blind in O. S. and could only count fingers in the nasal field of O. D. He was still very lethargic and apathetic, lacking in spontaneity, but oriented. In July, 1954, he had an epileptic seizure with convulsive movements of the left arm and loss of consciousness. (He had had two previous fits shortly after his second operation.) He was now very emotional, weeping and having outbursts of uncontrollable anger, which frightened his wife. His memory for names and places was poor, and his thinking was slow.

In February, 1955, he was readmitted for further evaluation. Psychiatric examination was recorded as follows:

"The patient is sitting in a chair, cooperative and attentive to questions. When asked if he has financial worries, he says 'yes,' and then goes on to tell how his wife is at work, with great circumstantial detail, and continues talking steadily, slowly, and monotonously, almost as if in a slow flight of ideas, one association leading on to the next.

"Insight is partial; he fears loss of his remaining sight if operated on.

"Orientation for time is good—'the day after Valentine's Day.' As to place, he knows he is in a hospital but can't think of the name: 'Cripes—I had that last night—I can't think of it. They repair you here. I was in bad shape (weeps). I was all alone in my room.' As to person, he answers correctly.

"Mood: Weeps easily. When asked the date, he says, 'I can't even see the calendar,' and weeps. Not primarily depressed, he says, 'I've always had good spirits,' but is easily turned to self-pity.

"General information: Poor. Does not know who is governor. President? 'Oh, cripes, I told that guy last night. The ex-President was that thin guy; he was president twice. A general is in there now.'

"Memory: Poor, especially for names. Can name his children but makes mistakes and calls them by the names of his siblings at times.

"Attention: Good, sticks to a train of thought rather doggedly but with slow reactions.

"Subtraction of serial 7's: Rather slow but without pauses: 93-85-77-60-53-44-35-28-21-14-7-0.

"The picture is one of cerebral defect, causing slowed reactions, dulled perceptions, poor memory, and circumstantiality with good attention and no confusion, delusions, or hallucinations."

COMMENT

These five case reports serve to show that pituitary tumors are capable of producing other derangements than their well-known alteration in endocrine function of the pars anterior and pressure on the optic chiasm. Complicating epileptic seizures have long been recognized as a sign of parasellar extension due to compression and irritation of the cortex of the temporal and frontal lobes (Jefferson [4]). Changes in autonomic control have rarely been observed, although there are occasional reports of disorder of sudomotor, vasomotor, and thermal control related to compression of the sympathetic centers in the anterolateral walls of the third ventricle or occurring after operation on lesions in this difficult area. Diabetes insipidus, from injury to the supraopticohypophyseal tract or pituitary stalk, is also not a frequent complication. On the other hand, somnolence and obesity are not uncommon.

Somnolence is likely to follow any diffuse compression of the brain with elevation of intracranial pressure. More specifically, it can be produced by injury to the structures lateral to the posterior walls of the third ventricle and upper portion of the Sylvian

aqueduct (Ranson and Magoun[32]; French[33]; Hess[34]).

Obesity is known to occur with lesions of the floor of the third ventricle (Ranson[32]). Our second patient became progressively somnolent, and finally unrousable during the last month of her life, although hydrocephalus had been relieved by a drainage procedure and autopsy showed no evidence of injury to the midbrain reticular formation. She also developed a voracious appetite, but without increase of her long-standing obesity. Our last two patients also had periods of hypersomnolence, but to a less striking degree.

Recognition of the significance of pyschological disturbances has been long overdue, if for no better reason than that these indicate an incurable lesion with extension far up into the third ventricle or forward between the frontal lobes. Their early recognition might lead to effective surgical treatment. The first and most consistent symptom is dullness; the patient slows down in his mental processes and begins to be apathetic. Any brain tumor may cause this in slight degree by raising the general intracranial pressure or by compressing the frontal lobes, but in these pituitary tumors the apathy seems to be more marked and more specific. Of our five cases, all but Case 1 showed this definitely; in the first case it was slight and only of the degree often seen in patients after a frontal leucotomy. In Case 4 there was great variation in awareness of environment, attention, and ability to concentrate. At times he was apathetic, but at other times active and aggressive. Variation in the level of awareness was noted in all five cases; all showed periods of apathetic behavior, alternating with better awareness and alertness when aroused. But even then it was as if the responses to stimuli were made with an effort, slowly and repetitively (especially in Cases 2 and 5).

Loss of memory was an important symptom in three cases (2, 4, and 5). In Case 2 it led to marked confabulation. The loss was largely for recent events and immediate retention, but in the end-stages it became more complete (Cases 2 and 4). This does not necessarily have to be considered a special symptom, but may be related to the loss of ability to take in the immediate environment quickly and clearly.

There was clear evidence of hallucination in only the second and fourth patients. Delusions were obvious in three cases, with a paranoid trend in two (Cases 3 and 4). Case 1 stands out as showing no delusions or memory loss (Table 2). The clinical picture of this patient resembled that of a person with an extensive frontal leucotomy, and it is of interest that the tumor extended forward between the frontal lobes, as well as backward and upward, effectively blocking most of the frontothalamic paths.

TABLE 2.—*Distribution of Psychological Symptoms*

	Case				
	1	2	3	4	5
Convulsions	+	..	..	..	+
Irritability, restlessness	+	..	+	..	..
Belligerence or profanity	+	..	..	+	..
Poor judgment	+	+	..	+	+
Delusions or hallucinations	..	+	+	+	?
Paranoid or suspicious tendency	..	..	+	+	..
Loss of memory	..	+	+	+	+
Confabulation	..	+	..	+	..
Difficulty in concentration and attention	..	+	..	+	+
Dullness, slowness, or apathy	+	+	+	+	+
Somnolence	..	+	+	..	..

Our five patients illustrate the sort of symptoms for which one should be watchful. Table 2 shows the general distribution of these symptoms.

In an attempt to classify these changes, it seems justifiable to attribute loss of concern for and comprehension of the present situation to compression of the frontal lobes. This was a striking feature in our first case and, to a less degree, in the last patient, who seemed quite unconcerned over his increasing blindness. In a recent patient with a large midline oligodendroglioma, which grew upward from the floor of the anterior fossa, compressing the medial surface of both frontal lobes, a similar "postlobotomy" syndrome disappeared after a very radical resection of the tumor. This man, likewise, had been quite unconcerned about his increasing blindness and did not consult a

doctor until he crashed his car into a traffic island. On the other hand, hypersomnolence, at least in the absence of an elevated intracranial pressure, is probably due to tumor extensions compressing the walls of the posterior portion of the third ventricle. Our second patient became strikingly somnolent during the last two months of her illness and impossible to arouse during the final two weeks. The caudal extension of this adenoma into the posterior portion of her third ventricle is clearly shown in Figure 3. The other four patients all had periods of drowsiness. Injury to this area, as was clearly described by Williams and Pennybacker,[29] may also lead to a clinical picture resembling Korsakoff's syndrome (Victor and Adams[35]). This is of interest to the present discussion because the syndrome described by Korsakoff and by Wernicke has as its mental manifestation the amnestic-confabulatory phenomenon, with lesions found symmetrically about the third ventricle, aqueduct, and upper fourth ventricle. In alcoholism the lesions are due to vitamin deficiency; in our cases they may be due to pressure. "Confusion" is also commonly described as a part of these syndromes. It is not of primary importance, however, because it is probably explainable on the ground of marked amnesia.* When a person can retain memories for only a few minutes, it is obvious that he easily becomes confused. These patients all had tumors of such size that both the frontal lobes and the structures lying adjacent to the posterior portion of the third ventricle could have been involved. Their psychological abnormalities tended to be a mixture of the two types. The first patient presented the clearest-cut syndrome of the frontal lobe, and the second and fourth, the greatest evidence of posterior third ventricle involvement.

We have had one operative death, but the four surviving patients have had no remission of their psychological disturbances after repeated operative interventions. Results of surgery were disheartening even in respect to eyesight and headache. Improvement, though definite, was short-lived in Case 2, and no improvement in vision was obtained in the last three.

Mortality in large extrasellar adenomas has been as high as 33% and 35% in the competent hands of Jefferson[4] and Olivecrona (Bakay[3]). This is similar to our experience with other patients with adenomata expanding upward in this region who did not have complicating mental changes. With so little success from our surgical attempts, we are reluctant to recommend removal when a solid tumor fills the third ventricle. In cases with forward extension between the frontal lobes, operation may be worth while if a very radical resection is carried out. This entails an extensive removal of the tip of the nondominant hemisphere.

In the pituitary adenomas, particularly the chromophobe variety, the first essential is to detect the tendency to suprasellar extension before the lesion reaches a formidable size. This can only be achieved by early pneumoencephalography and periodic repetitions, as recommended by Bakay and White.† The present enthusiasm for radiation therapy tends to make neurologists omit the pneumoencephalogram in early cases, in which it can be of greatest value.

In the case of craniopharyngiomas, the chances of palliation are better, as the cysts can be evacuated by the usual transfrontal route. When a very large suprasellar cyst extends upward into the third ventricle, producing hydrocephalus, the lesion may be attacked as an intraventricular cyst. Dott (Clark, Beattie, Riddoch, and Dott[36]) has recorded several instances of successful

* It is of interest to point out that memory may also appear to be lost when there is bilateral compression of the frontal lobes, because the frontal-lobotomized patient is often so apathetic that he will not make the effort to recall past events.

† Reference 31. Incidentally, this procedure should be accredited to Jefferson, though he never specifically described the method. His 1940 presidential address before the Royal Society of Medicine contains a beautiful pneumoencephalographic visualization of a large suprasellar adenoma compressing the third ventricle.

evacuation of craniopharyngiomas with removal of the cystic wall in the third ventricle. This was accomplished by incision through the thinned cortex and white matter of the frontal lobe and enlargement of the foramen of Monro. When the hydrocephalus cannot be relieved by removal of the obstructing portion of the cyst, or when an adenoma has pushed up into this position, the pent-up cerebrospinal fluid can be drained by Torkildsen's method of ventriculocisternostomy. In Case *2* we resorted to Nosik's ventriculomastoidostomy instead, because the patient was too sick to tolerate the more major procedure in the posterior fossa. Ordinarily Nosik's procedure is less desirable, because of the risk of subsequent otitis and occasional blockage of the tube. Radiation in our experience has not been effective in reducing the size of these giant suprasellar neoplasm.

SUMMARY AND CONCLUSIONS

In addition to endocrine and visual disturbances, hypophyseal tumors may give rise to serious psychological abnormalities. This complication is seen more frequently with the chromophobe adenomas and craniopharyngiomas, although the eosinophilic adenomas may rarely develop large suprasellar extensions. Five examples of this unusual syndrome are described.

As the tumors expand above the diaphragma sellae and compress the walls of the third ventricle or the frontal lobes of the brain, the mental changes consist of dullness, progressing to somnolence and apathy, with difficulty in concentration. There may also be loss of retention and memory, leading to confusion and sometimes confabulation. When aroused, the patient may be irritable, aggressive, and active. Poor judgment is common, and delusions and hallucinations may occur.

These signs indicate that there has been a large suprasellar extension of the growth, either forward, between the frontal lobes, or upward and backward, into the third ventricle. With distention of the latter, hydrocephalus may occur from blockage of the outflow of fluid from the lateral ventricle. With extension upward and backward, the amnestic-confabulatory syndrome with somnolence is to be expected. In contrast, when the tumor separates and compresses the frontal lobes, it is likely to produce a syndrome similar to that seen after an extensive bilateral lobotomy. Convulsive seizures may also supervene, especially when extension is forward between the frontal lobes or laterally into a temporal lobe.

These signs indicate a giant parasellar extension. The chances for improvement are poor for mental symptoms, for visual recovery, or for relief of headache, regardless of whether treatment is by irradiation or surgery. Ultimately, with further growth of the neoplasm, there is progressive deterioration to a vegetative state, with increasing drowsiness and finally coma and death.

Before a chromophobe adenoma is treated by irradiation, the degree of suprasellar extension should be visualized by pneumoencephalography. All the adenomas with suprasellar extension should be followed by repeated air studies and operated upon before the tumor reaches a prohibitive size.

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The Sedation Threshold, Manifest Anxiety, and Some Aspects of Ego Function

CHARLES SHAGASS, M.D.
and
JAMES NAIMAN, M.D., Montreal, Canada

The sedation threshold is an objective pharmacological determination, which depends upon EEG and speech changes produced by intravenously given amobarbital (Amytal) sodium.[1] This procedure was developed to measure manifest anxiety,* and its validity for this purpose was demonstrated in two studies of psychoneurotic patients.† The main purpose of the present investigation was to determine whether the sedation threshold also measures manifest anxiety in nonpatient controls and in certain psychotic disorders.

There have been no previous attempts to correlate clinical findings in a control group with the sedation threshold. In another study,[2] thresholds of the present control group were compared with those of psychoneurotics. Hysterical patients were the only neurotic group with thresholds similar to those of controls; in all other neurotic groups the threshold was significantly higher. Previous investigation of the sedation threshold in psychosis has been confined to the study of a group of 11 schizophrenics.[1] No clear relationship between the threshold and the degree of manifest anxiety was found in that group. However, it appeared that recency of psychosis might be an important determining factor, since the thresholds of acute cases were lower than those of equally tense chronic cases.

The psychotic patient groups studied here represented acute schizophrenias, chronic schizophrenias, agitated depressions, and organic mental syndromes. Choice of psychoses for study was partially governed by the hypothesis that, in addition to manifest anxiety, the sedation threshold is influenced by factors involved in impairment of ego functions.‡ This hypothesis was based on initial results with schizophrenics,[1] and on the fact that barbiturates impair ego functioning, as well as diminish anxiety. According to the hypothesis, if the degree of manifest anxiety is held constant, the sedation threshold should be lower where there is greater impairment of ego functions. A crucial test of this hypothesis cannot be made in the absence of a valid independent measure of ego impairment. However, using the gross criteria of ego impairment, which are afforded by differences among groups of psychoses, it was possible to test two predictions based on the hypothesis.

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From the Allan Memorial Institute of Psychiatry and McGill University.

* "Manifest anxiety" refers to anxiety judged present from direct evidence obtained by clinical psychiatric examination. The qualifying term, "manifest," is used to avoid confusion with such concepts as "unconscious anxiety."[3]

† References 1 and 2.

‡ The concept of ego function is difficult to circumscribe. Green [4] has recently compiled a list of 10 major ego functions. For present purposes, "ego function" is used to indicate a group of functions, such as reality contact and judgment, which become grossly impaired in psychotic disorders.

The first prediction concerned the difference between acute and chronic psychoses. In psychoses of recent and acute onset there is usually marked impairment of ego functioning as compared with the prepsychotic state. In psychoses of longer duration there is still impairment, but, provided the patient has not deteriorated, some reorganization or repair of ego functioning takes place.[5] Consequently, since greater impairment of ego functions is more likely in acute than in chronic psychoses, the present hypothesis would predict lower sedation thresholds in the former. This prediction was tested by comparing the thresholds of patients with acute schizophrenia and agitated depressions and those of patients with chronic schizophrenia.

The second prediction concerned the organic psychoses. Gross impairment of accepted ego functions, such as orientation, memory, and comprehension, is among the cardinal signs of organic mental states. Since the extent of such changes is greater in these states than in any others, one would predict from the present hypothesis that organic psychoses should show the lowest sedation thresholds of any group. This prediction was tested by comparing the organic group with all others.

METHODS AND MATERIALS

Sedation Threshold Procedure

The method has been described in detail elsewhere.[1] Amobarbital sodium is given intravenously at the rate of 0.5 mg/kg. of body weight every 40 seconds. The patient is tested for slurred speech, and the injection is continued at least 80 seconds after slurred speech is noted. Continuous EEG's are recorded from transverse frontal and sagittal frontocentral placements. Amobarbital sodium nearly always produces an increase of 15 to 30 cps activity in these areas (Fig. 1). The amplitude curve of the 15 to 30 cps activity usually contains an inflection point, coinciding with the time when slurred speech is first noted (Fig. 1). The sedation threshold has been defined as the amount of amobarbital sodium, milligrams per kilogram of body weight, required to produce this inflection point, in association with slurred speech.

Measurements are usually made from the transverse frontal tracing, but if there is too much muscle artifact, the sagittal frontocentral tracing is used. A technically valid sedation threshold is obtained in about 9 of 10 tests. The measurement is highly reliable; its probable error is no greater than 0.5 mg/kg. of body weight.[2] Age, sex, and previous intake of sedatives, in usual psychiatric dosage, have not been found to influence the threshold.

Subjects

(*a*) *Controls.*—There were 45 control subjects, 34 men and 11 women; 41 were volunteer military personnel, and the remainder were graduate nurses. Ages ranged from 17 to 45 years, with a median of

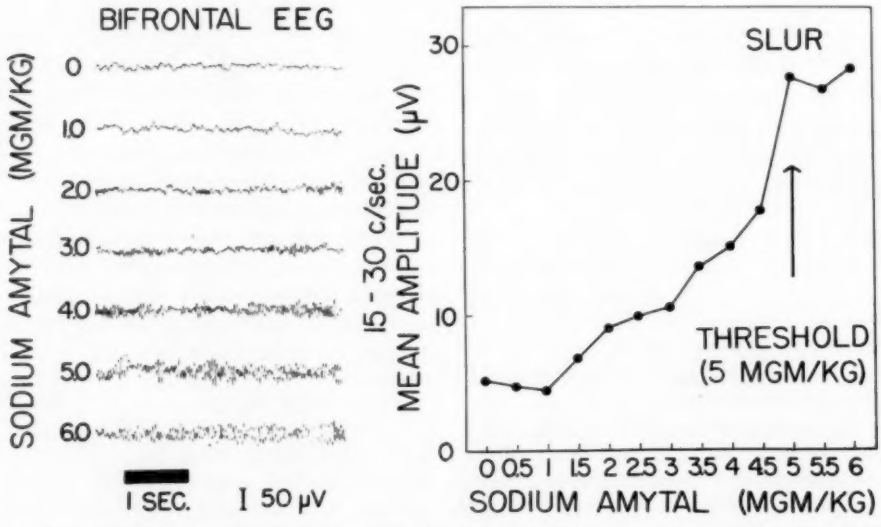

Fig. 1.—Effect of increasing amounts of amobarbital (Amytal) sodium on bifrontal EEG. Note inflection point in amplitude curve, which coincides with slurred speech.

21.2 years. An attempt was made to obtain volunteer subjects with good mental health records. This attempt was not completely successful, since examination revealed some evidence of emotional disturbance in a fair proportion of the subjects.

(*b*) *Acute Schizophrenia.*—There were 11 patients in this group, 6 men and 5 women. Ages ranged from 21 to 42 years, with a median of 20 years. At time of testing, the duration of overt psychotic symptoms, usually of sudden onset, ranged from 1 to 16 weeks, with a median duration of 2 weeks.

(*c*) *Chronic Schizophrenia.*—The term "chronic" is used here in the sense of long duration of illness. Most of the patients were not deteriorated, and only 4 of 34 had ever been committed to a mental hospital. No borderline or doubtful cases were included in this group. All showed definite features of schizophrenia. There were 22 men and 12 women. Ages ranged from 16 to 46 years, wih a median of 23 years. The duration of illness ranged from 9 months to over 20 years; the median was about 4 years. Of the 34 patients with chronic schizophrenia, 6 had a simple and 12 a predominantly paranoid form. The remaining 16 had mixed types, showing features of more than one subtype.

(*d*) *Agitated Depressions.*—There were 14 men and 8 women in this group. Ages ranged from 28 to 74, with a median of 49 years. Duration of the present illness ranged from two weeks to two years; median duration was about four months. Six patients showed symptoms resembling those of schizophrenia, in addition to depression; for these the probable diagnosis was schizoaffective psychosis. Our purpose in using agitated depressions was to obtain a group of depressions which would be likely to match the schizophrenia groups in degree of manifest anxiety.

(*e*) *Organic Psychoses.*—This group contained 11 patients, 7 men and 4 women. Ages ranged from 38 to 78; the median age was 57 years. Duration of mental symptoms ranged from 1 month to over 13 years; median duration was about 18 months. Symptoms were attributed to the following underlying conditions: cerebral arteriosclerosis, four cases; dementia paralytica, three cases; presenile dementia, two cases; senile dementia and Wernicke's encephalopathy, one case each.

Clinical Evaluation Procedures

(*a*) *Interview of Controls.*—Of the 45 control subjects, 44 were interviewed by one psychiatrist or by two psychiatrists jointly. The interview lasted about 30 minutes and covered personal and family histories, together with detailed inquiry into somatic complaints, phobias, and obsessional and depressive trends. Sexual history was not covered, for administrative reasons. The interview was conducted prior to the sedation threshold test, and the findings were dictated within two hours. After the control series was completed, the investigator, who had not participated in most of the interviews, reviewed the typewritten notes and scored them on a 0 to 2+ scale, according to the number of symptoms indicating adult psychopathology which had been elicited. Childhood symptoms were disregarded. The zero rating was assigned to a completely negative history. Histories containing a single minor complaint, such as occasional restless sleep, mild obsessional trend, rare headaches, or mild tenseness under stress, were rated plus-minus (±). A 1+ rating was given to those histories containing a single definite symptom, such as insomnia, persistent nail biting, palpitations for no reason at all, a phobia (other than fear of heights, which seemed nearly universal), frequent tension headaches, etc. In addition, excessive overt tension during the interview, as indicated by marked sweating or gross tremor, was counted as a symptom. Two-plus (2+) ratings were given to subjects reporting two or more definite symptoms, or a history of previous neurotic illness, or a history of requiring sedation for a single period of at least one month. As a check upon the reliability of this scoring scale, a psychiatrist who had seen none of the patients was asked to review the clinical notes and to score the records independently. The correlation between the two raters was approximately +0.8. Disagreement was never greater than one scale point. Since the symptoms elicited were mainly overt manifestations of anxiety, this scale may be taken as a fairly reliable clinical criterion of manifest anxiety.

(*b*) *Saslow Screening Inventory.*—This inventory was administered to 43 of the 45 control subjects. It is a self-administered questionnaire,[6] which takes from 5 to 10 minutes to complete, and was found by Ulett and associates[7] to correlate as well with certain physiological indices of anxiety proneness as the opinion of a team of psychiatrists and clinical psychologists. The inventory was scored by a method described by Gleser and Ulett.[8] The higher the score, the more complaints, suggestive of anxiety proneness, reported by the subject. To obtain some indication of the expected findings in the kind of psychiatric patient population studied here, the inventory was also administered to 30 randomly selected patients. Scores of these 30 patients were markedly higher than those of controls; medians were 6.0 and 2.6, respectively. Five of the 30 patients (17%) fell below a score of 3.1, as opposed to 29 of the 43 controls (67%).

(*c*) *Rating of Tension in Patients.*—The clinical procedure used for rating tension was described in a previous report.[1] Most of the patients were rated by this method. Ratings were made prior to testing. Ratings were on a 5-point scale; a rating of 5

indicated the highest possible degree of tension; a rating of 1, the lowest degree of tension. If both investigators participated in the interview, the mean of their ratings was used.

RESULTS

A. Control Group

The percentage distribution of sedation thresholds in the control group is shown in the upper curve of Figure 2. The distribution is almost symmetrical and essentially follows the pattern of a normal curve. The mean threshold was 3.09 mg/kg., and the median was 3.03. Thresholds of men and women were almost identical; medians were 3.04 and 3.00, respectively.

After the control sample had been tested, the question was raised as to whether the sample was large enough. As a partial answer to this question, the male group was divided in two, and the distribution of thresholds for the first 17 subjects tested was compared with that for the next 17. The two distribution curves are shown in the lower part of Figure 2. They are almost identical. This consistency of distribution suggested that little would be gained from enlarging the sample, and that the sample was reasonably representative of the population from which it was drawn.

Correlation with Interview Findings.—The upper part of Figure 3 shows the relationship between the sedation threshold and the rating of psychiatric symptoms elicited during interview. The bars show the proportion of cases in each rating category with sedation thresholds of 3 mg/kg. or less and 3.5 mg/kg. or more. Among control subjects with a relatively negative history (rated 0 or ±), the sedation threshold was 3 mg/kg. or less in 90%; similarly low thresholds were

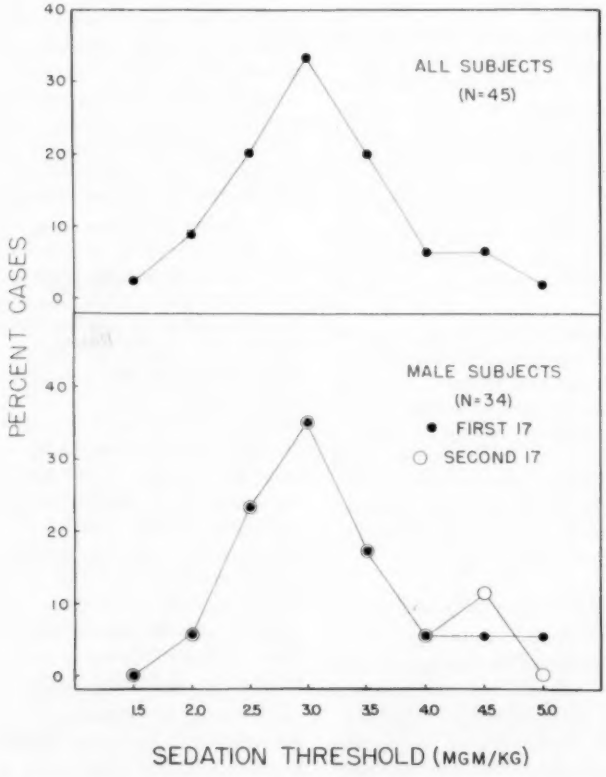

Fig. 2.—Percentage distributions of sedation threshold in control subjects. Above: entire group; below: comparison of distributions in first and second halves of male group.

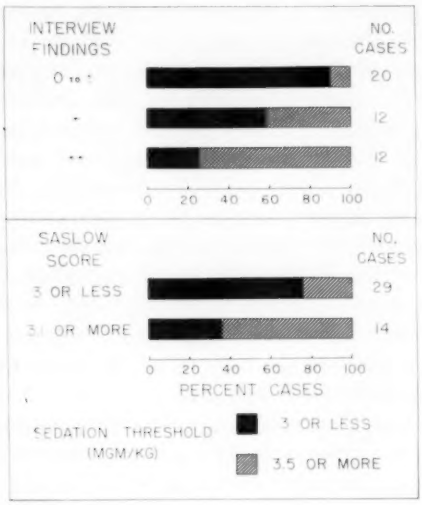

Fig. 3.—Relationship of sedation threshold to clinical findings in control group. Above: interview findings; below: Saslow screening test results.

found in only 25% of subjects with a 2+ history. The relationship in Figure 3 was highly significant statistically (χ^2 16.3; $P < 0.001$).

Individual clinical observations agreed well with expectations based on data from psychiatric patients. The single subject with a threshold of 5 mg/kg. was a schizoid young man who was a severe nail biter, complained of headaches and palpitations, and believed that people on the street looked at him and laughed at him. The average anxious borderline schizophrenic in our series had a sedation threshold in the neighborhood of 5 mg/kg. Subjects who reported complaints of a hysterical nature usually had a low threshold; e. g., one man who had consulted a psychiatrist about being excessively ticklish had a threshold of 2.5 mg/kg. This agrees with findings in cases of overt hysterics.[2]

Correlation with Saslow Score.—The lower part of Figure 3 shows the relationship between the sedation threshold and the Saslow score. This relationship is not as striking as that obtained with the interview findings. The χ^2 for the fourfold division in Figure 3 was 6.1 ($P<0.02$). These results suggest that the more symptoms reported in the questionnaire, the higher the sedation threshold.

Age.—There was no significant correlation between age and sedation threshold in the control group.

Comment.—These results with control subjects are, in general, similar to those obtained with psychoneurotic patients. They indicate that in nonpatient subjects the sedation threshold rises as the degree of manifest anxiety increases.

B. Psychotic Groups

Correlation with Tension Rating.—Tension ratings were available for 68 of the 78 psychotic patients. They were missing for six with organic psychoses, 2 with agitated depressions, 1 with acute schizophrenia, and 1 with chronic schizophrenia. The relationship between the tension rating and the sedation threshold for the entire group is shown in Table 1. Although there was a trend toward a positive correlation, it was not a strong one. The χ^2 value, computed for a 2×2 table derived from Table 1, was 3.78; this just misses the 5% level of confidence.

An attempt was made to discover possible correlations between the tension rating and the sedation threshold within each individual group. None was found in the agitated depression group. There was a slight trend

Table 1.—*Tension Rating* vs. *Sedation Threshold for All Psychotics*

Tension Rating	Sedation Threshold (Mg./Kg.) <2.5	2.5-3	3.5-4	4.5-5	5.5+	Total
<3	3	6	1	0	1	11
3-3.5	5	6	6	2	2	21
3.75-4.25	2	6	7	1	2	18
4.5+	1	5	4	5	3	18
Total	11	23	18	8	8	68

Table 2.—*Tension Rating* vs. *Sedation Threshold for Chronic Schizophrenics*

Rating	Threshold (Mg./Kg.) <4.5	4.5+	Total
<4.25	15	2	17
4.25-5	6	10	16
Total	21	12	33

in the acute schizophrenics, but the group was too small to permit statistical appraisal. The organic group was also too small. In the chronic schizophrenic group there was a statistically significant relationship ($P<0.01$) between the tension rating and the threshold. This relationship, which is shown in Table 2, indicates essentially that those chronic schizophrenic patients, who appeared to be exceedingly tense, tended to have very high thresholds.

These results indicate that there is less correlation between the sedation threshold and clinical evidence of tension in psychotics than in normal subjects or in neurotics.

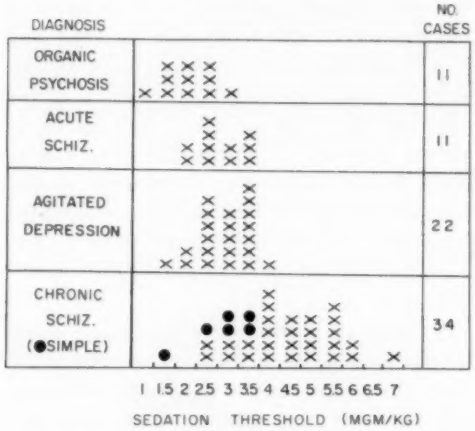

Fig. 4.—Frequency distributions of sedation thresholds in four groups of psychoses. Simple schizophrenias are indicated by solid circles in chronic schizophrenic distribution.

Among the factors contributing to this divergence of results in psychotics, an important one appears to be connected with the differences among the various psychotic groups.

Difference Among Groups.—Figure 4 shows the frequency distributions of sedation thresholds for the four psychotic groups. The means of these distributions, in milligrams per kilogram, were as follows: organic psychosis, 2.00; acute schizophrenia, 2.77; agitated depression, 2.91; chronic schizophrenia, 4.22. The following statistically significant differences among groups ($P<0.01$) are relevant to the two predictions from the hypothesis that the threshold measures ego impairment: 1. Thresholds of the chronic schizophrenics were significantly higher than those of the agitated depression group and of the acute schizophrenics. This indicates that psychoses of long duration are associated with higher thresholds than are acute psychoses. 2. Thresholds of the organic psychoses group were significantly lower than those of the other psychotic groups. They were also significantly lower than those of the control group. This finding bears out the prediction that the group with the greatest impairment of ego function would have lower thresholds than any other.

Mean tension rating for the chronic schizophrenic group was 3.91 mg/kg., which was not significantly higher than the mean ratings of 3.65 mg/kg. for the acute schizophrenic group and 3.71 mg/kg. for the agitated depression group. Since these groups were similar with respect to amount of tension detectable by an examiner, the differences in sedation threshold appear attributable to other factors.

Simple Schizophrenia.—Sedation thresholds of the six patients with simple schizophrenia are shown separately in Figure 4. These were all below the median. The group was thought to be somewhat less tense than the other patients; the mean of the five available tension ratings was 3.3 mg/kg. So far, simple schizophrenia is the only subtype which appears separable from other chronic schizophrenias in terms of sedation threshold. If confirmed, this observation will be of theoretical interest, because this subtype is characterized clinically by relative absence of "restitutional" symptoms.

Age.—Since the groups differed considerably in age, it is necessary to consider the extent to which this factor may have influenced the results. Ages of the acute and of the chronic schizophrenic group were similar, so that their different thresholds cannot be attributed to age difference. The agitated depression group was older than the chronic schizophrenic group. However, within each of these groups there was no relationship between the threshold and age. The organic group was the oldest, but it was possible to

compare sedation thresholds of 9 of the 11 patients with organic psychoses with those of 9 with agitated depressions of the same age. The mean threshold of these 9 depression patients was significantly higher than that of the 9 patients with organic psychoses (3.2 mg/kg., compared with 2.3 mg/kg.). It seems reasonable to conclude that the age factor was not a significant determinant of present results.

COMMENT

Results of this investigation support the conclusion that the sedation threshold is a valid measure of manifest anxiety in nonpatient control subjects. In psychotics the correlation between the threshold and the degree of manifest anxiety was considerably less clear than in controls and in psychoneurotics. As a method of measuring manifest anxiety, the procedure thus seems applicable mainly to nonpsychotic subjects. This is not to say that degree of manifest anxiety is unrelated to the sedation threshold in psychotics, since some correlation was demonstrated here. However, in psychosis, other factors, such as degree of impairment of ego functions, appear to influence the threshold at least as much as does manifest anxiety.

Present results bore out two predictions made from the hypothesis that impairment of ego functioning lowers the sedation threshold. As predicted, patients with acute psychoses had lower thresholds than equally tense chronic cases; also, a group of patients with organic psychoses had lower thresholds than all other subject groups. These findings support the hypothesis and offer some explanation for the different correlations between sedation threshold and manifest anxiety in psychotic and in nonpsychotic subjects. It appears that the threshold correlates highly with at least two factors, manifest anxiety and ego impairment. One raises the threshold; the other lowers it. In nonpsychotic subjects, variation in degree of manifest anxiety is far greater than variation in degree of gross ego impairment; correlation with manifest anxiety then becomes easy to demonstrate. In psychotics there is considerable variation in degree of ego impairment, and the influence of this factor on the threshold may overshadow the effect of the manifest anxiety factor.

The possible effect of the ego impairment factor on the threshold in nonpsychotic subjects is difficult to assess. Certain aspects of the data suggest that there may be some effect. Sedation thresholds of controls were significantly lower than those of psychoneurotic patients.[2] This difference, while considerable, was still not as great as might be expected from the relative amounts of manifest anxiety in these groups. The discrepancy between actual and expected threshold differences lies in the fact that neurotics have more symptoms than controls with the same threshold. If one assumes greater ego impairment in the neurotics, as is likely on clinical grounds, this discrepancy may be understood. The threshold would be decreased by ego impairment; consequently, for a given degree of manifest anxiety, neurotics, with greater ego impairment, would have lower thresholds than controls.

Applications of the Sedation Thresholds.—An objective method of measuring anxiety is greatly needed for many important problems in psychiatric and psychosomatic research. Apart from the problem of quantifying anxiety, a major research difficulty stems from the probability that the term "anxiety" is used to designate a number of reactions which, although psychologically similar, may be neurophysiologically different. Elsewhere,[2] it has been proposed that tests like the sedation threshold might be used to distinguish objectively between different types of anxiety, much as the leuocyte count is used to distinguish between different causes of fever. It has proved worth while to apply the method to clinical and research problems along such lines at this Institute.§

The finding that the sedation threshold correlates with degree of ego impairment, in addition to manifest anxiety, imposes certain restrictions upon its application as a clinical and research tool. As a measure of manifest

§ References 2 and 9.

anxiety, its use seems limited to nonpsychotic subjects. On the other hand, there are some important practical implications of the correlation with ego impairment. It is often difficult to distinguish clinically between neurotic and psychotic depression. This distinction is readily made by the sedation threshold; the psychotics have low thresholds, the neurotic depression group have high ones.[10] Also, the very low thresholds found in organic psychosis may sometimes provide a useful sign in support of the diagnosis.

Recent studies by Weinstein and his collaborators || are of interest in connection with the concept that the sedation threshold is related to impairment of ego functions. Their work shows that amobarbital sodium can elicit latent patterns of disorientation and denial of illness in patients with brain disease. Such "organic" signs are not elicited in persons without brain disease. This property of amobarbital sodium may be used as a test for diagnosing and following the progress of organic brain disorders. Some observations, similar to those of Weinstein and associates, were made on organic psychoses during the course of the present study. Weinstein and colleagues suggest that amobarbital sodium has an additive action in increasing the effect of the structural lesion on brain metabolism. In terms of impairment of ego functions, one would say that the drug increases impairment produced by the lesion.

Neurophysiological Considerations.—Some neurophysiological implications of the correlation between the sedation threshold and the degree of manifest anxiety have been discussed in previous papers.¶ Since the reticular systems of brain stem and thalamus are especially sensitive to the effects of barbiturates,[13] the results were interpreted to indicate that these systems play an important role in mediating anxiety. The role of the reticular systems in mediating activities, which may be classed as ego functions, e. g., attention, is better established than their relationship to anxiety. Jasper gave early recognition to the part played by these systems in complex behavior in his 1949 paper, "The Integrative Action of the Thalamic Reticular System." [14] Much neurophysiological evidence has accumulated since to support the thesis that adequate reality contact requires intact reticular system functioning.

Since barbiturates cause widespread suppresion of reticular system activity, this mechanism probably accounts for the diminution of anxiety and impairment of ego functioning which these drugs produce. In relation to barbiturate effects, manifest anxiety and ego impairment thus seem to involve the same neural mechanisms. This is not surprising, since, although they have been treated separately here for heuristic purposes, they often appear closely related, e. g., when intense anxiety impairs ego functioning. However, manifest anxiety and ego impairment are not identical, and present data suggest that they may vary independently, even as regards response to barbiturates.

Recent studies indicate that the reticular formation cannot be regarded as a functional unity; it is probably composed of a number of functional systems. Rothballer # has obtained evidence of a distinct adrenergic component. This adrenergic component seemed more sensitive to barbiturates than other components, although all were sensitive. Rothballer's observations may provide some basis for understanding the relationships and differences between manifest anxiety and ego impairment. It is likely that different components of the reticular systems are involved in each, although there may be some overlapping. The component mediating anxiety may be related to the adrenergic one, in which case it would be more sensitive to barbiturates than the component or components involved in ego functioning. This inference is supported by the fact that when

|| References 11 and 12.

¶ References 1 and 2.

Rothballer, A. A.: Adrenergic Component of the Reticular Activating System, presented at the Research Conference in Psychopharmacology, McGill University, March 26, 1955.

barbiturates are effectively used for daytime sedation, anxiety is suppressed without impairing ego functioning. With increased amounts of drug, greater portions of the reticular systems are affected, and ego functioning is impaired.

The role of the reticular systems has been emphasized in the preceding discussion. Other brain areas are undoubtedly also important in mediating the functions under consideration. However, it is possible that the phenomena related to the sedation threshold may be most readily understood in terms of reticular system function.

SUMMARY

The sedation threshold is an objective pharmacological determination which depends upon the EEG and speech changes produced by intravenous amobarbital (Amytal) sodium. It has been shown to measure degree of manifest anxiety in psychoneurotics. The present investigation was carried out for two purposes: (*a*) to determine whether the threshold measures manifest anxiety in nonpatient, control subjects and in certain psychoses, and (*b*) to test two predictions, based on the hypothesis that impairment of ego functions, such as reality contact, lowers the sedation threshold.

In 45 nonpatient (control) subjects there was a high positive correlation between the sedation threshold and the number of symptoms of manifest anxiety elicited in a psychiatric interview. There was also a significant relationship between the threshold and the score on a self-administered symptom inventory (Saslow Screening Test).

Psychotic patients include 11 with organic psychoses, 11 with acute schizophrenia, 22 with agitated depressions, and 34 with chronic schizophrenia. In the psychotic group as a whole there was no statistically significant correlation between the sedation threshold and clinical appraisals of degree of tension or manifest anxiety. Among the chronic schizophrenics there was a significant positive correlation, which was smaller than that found in psychoneurotics or in controls.

From the ego impairment hypothesis, it was predicted that the chronic schizophrenic group would have higher thresholds than apparently equally tense patients with acute schizophrenia or agitated depressions. It was also predicted that the organic psychoses group would have lower thresholds than any other subjects. The results confirmed both predictions.

It is concluded that the sedation threshold is positively correlated with degree of manifest anxiety and negatively correlated with degree of impairment of ego functioning. Since the ego impairment factor is important mainly in psychotics, it was concluded that the sedation threshold, as a measure of manifest anxiety, is most applicable to nonpsychotic subjects. Other applications of the procedure are considered.

The findings are discussed in relation to recent neurophysiological evidence concerning differential sensitivity to barbiturates of different components of the reticular systems.

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The Effect of Hydrocortisone on the Healing of Wounds of the Brain

An Experimental Study on the Cat

ARMANDO ORTIZ-GALVAN, M.D., México, D.F.

The literature concerning the effects of the adrenal steroids cortisone and hydrocortisone on tissues and systems is exhaustive. Hydrocortisone U. S. P. (17-hydroxycorticosterone; Compound F) has been reported to be more potent, milligram by milligram, than cortisone,[1] and the main physiologic actions of the two are similar.[2] Hydrocortisone used in local application allows a higher concentration of the hormone in the tissue, and the difference in local effectiveness as compared with that of cortisone remains unexplained.[3]

Wound healing is delayed by cortisone,* and several tissues have been reported to be affected in the healing process when the adrenocortical steroid is given in high doses parenterally,[7] by local application, by subcutaneous injection,[8] or subconjunctivally.†

The action of cortisone in the healing of the central nervous system as noted experimentally has been observed to be a depression of the early inflammatory phase in puncture wounds of the brain in guinea pigs in which a state of hyperadrenalism has been induced by the administration of 2.5 mg. of cortisone four days prior to the production of the wound and daily doses of the drug intramuscularly until death, for up to 12 days.[11] In the prevention of meningocerebral cicatrix in experimental wounds of the brain in dogs and cats, cortisone given parenterally was found to be of no value.‡ A study of the action of corticotropin (adrenocorticotropic hormone of the anterior pituitary) in brain wounds in rats suggested that the hormone delayed healing.[12] Intrathecal administration of hydrocortisone acetate in suspension in experimental animals diminished the meningeal inflammatory response to talc.[13] Other studies of the action of the adrenocortical steroids in healing of the brain or meninges have not been reported.

In the present experiment incised stab wounds of the brain were used to demonstrate the action of hydrocortisone on the cells of the brain and on the healing process.

MATERIAL AND METHOD

Thirty cats were used for this experiment: Sixteen had unilateral, and fourteen bilateral, wounds. The animals with unilateral wounds were divided into (*a*) control cats; (*b*) cats receiving hydrocortisone acetate § parenterally in a daily dose of 10 mg., starting three days prior to operation (these cats were on a free diet and weighed daily), and (*c*) cats in which 20 mg. of hydrocortisone acetate in powder form was applied to the wound. The cats with bilateral wounds had 10 mg. of hydrocortisone acetate in suspension applied on the left side only,

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From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute, Montreal, Canada.

* References 4 to 6.

† References 9 and 10.

‡ Beltran, G. P.: La Intervención del acetato de cortisona en los procesos cicatriciales posttraumaticos del sistema nervioso, Thesis, Universidad Nacional Autonoma de Mexico, Facultad de Medicina, 1953. Gibson, R. N.: The Effect of Cortisone in the Healing of Incised Cerebral Wounds, Thesis, McGill University, 1951.

§ The hydrocortisone acetate was supplied by Merck & Co., Ltd., Montreal, Canada, in saline suspension of Hydrocortone acetate and as hydrocortisone acetate powder.

the right side remaining in this way as a control. The hormone was administered in the commercial suspension instead of as a powder in order to decrease the dose and increase the surface of absorption of the hydrocortisone crystals.

A craniectomy was performed under sterile conditions. A dural flap was turned, and in each case the middle segment of the suprasylvian gyrus was wounded. An incision 1 cm. in depth and 8 mm. in length was made with a sharp knife. A piece of absorbable gelatin sponge U. S. P. 6×5 mm. was placed in the wound routinely as a hemostatic agent, as a reservoir for the hormone after application, and as a means of studying the absorption rate of the gelatin sponge in the wound. The dura was closed with 00000 nonabsorbable surgical (silk) sutures U. S. P., and care was taken to cover the wound with the flap and to keep it out of contact with the line of suture. No antibiotics were given to the animals.

The cats with unilateral wounds were killed at different periods after operation: 4, 8, 16, and 48 days. The cats with bilateral wounds were killed at 4, 8, 16, 48, 60, 75, and 90 days. One animal with the unilateral control wound and one with the parenteral administration of the hormone, and two of the unilateral wound group with local powder application and two of the bilateral wound group were killed for each period of time.

After perfusion through both carotid arteries with isotonic saline and 4% formalin, the brain was taken out, cut transversely in the middle of the wound, and half of it placed in 4% formalin, to be stained with hematoxylin-phloxine-saffron, cresyl violet, and Laidlaw's connective tissue method; the other half of the block was placed in Cajal's formalin-ammonium bromide for Hortega's silver impregnation method for microglia and astrocytes, and Cajal's gold chloride-sublimate method.

The pituitary gland was taken out and studied in animals that had topical application of the hormone. The adrenal glands were studied in the cats with unilateral control wounds and in those with parenteral administration of the hormone.

RESULTS

There was no gross or microscopic evidence of infection in the animals. When dural adhesions were formed, they were delicate and easily disrupted. They were away from the wound and the wound edges. This was true in both control and treated wounds, unilateral and bilateral. A core of connective tissue extending from the dura into the wound was present in the 75-day wounds on both sides.

Histology of the Wound

1. *Short-Term Cats* (4, 8, 16, and 48 days).—A. Control Cats: There was an early inflammatory reaction of normal evolution, as indicated by the presence of hemorrhage in the wound and the appearance of neutrophiles, phagocytes, and lymphocytes. Early fibroblastic proliferation was observed in the four-day wound. The gelatin sponge underwent gradual absorption over 16 days and had completely disappeared by 48 days. In the 48-day wound leptomeningocerebral cicatrix was present, and the fibroblasts intermingled at the edge with glial cells. Phagocytosis was seen at 4 days, and a maximal microglial reaction was found at 16 days. The glia showed regressive changes in the four-day wound, and gradual progressive changes were seen in older wounds. Gliosis was present by condensation, and an actual increase in the number of astrocytes was not proved.

B. Cats with Unilateral Wounds to Which 10 Mg. of Hydrocortisone Acetate Was Administered Parenterally Daily: The weight of the animals did not change appreciably. The adrenal glands did not show signs of atrophy on histological examination.

The general histological picture of the wound was basically the same as in Group A in the stages corresponding to the different time periods. The end-result was a thinner leptomeningocerebral cicatrix and the presence of a greater number of gitter cells with intracellular pigment. Behavior of the astroglia was the same as in Group A.

C. Cats with Unilateral Wounds to Which 20 Mg. of Hydrocortisone Acetate Powder Was Applied Locally: In the four-day wound there were few neutrophiles and little edema, and the gelatin sponge was to one side of the wound. The wound was filled up with red blood cells. Infiltration of the gelatin sponge with neutrophiles was seen in the 16-day wound, and fibroblastic infiltration was not seen until the 48-day period. Proliferation of the connective tissue was diminished at all periods. There was a slight collagen and reticulin barrier in the 48-day wound. This wound was unhealed, the gela-

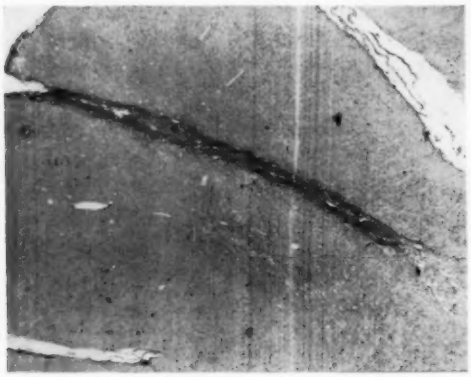
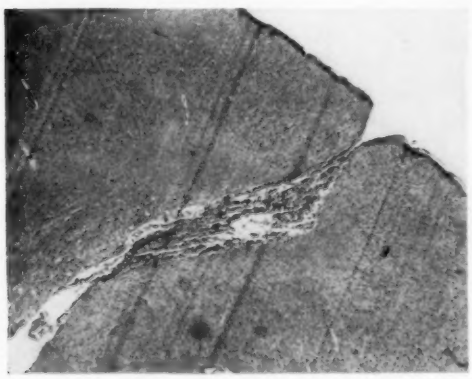


Fig. 1.—Bilateral wound; control side; 48 days. Leptomeningocerebral cicatrix. Hematoxylin-phloxine-saffron; reduced about ⅓ from mag. × 25.

tin sponge being still in place, with no evidence of absorption. The activity of microglia was diminished at all periods. The astroglia showed less regressive changes than in the control wound. The progressive changes of the glia were slight in the 48-day wound.

D. Cats with Bilateral Wounds (10 mg. of hydrocortisone suspension on the left side and wound control on the right): The wounds healed at different rates. At four and eight days, the inflammatory reaction, judged by the amount of edema, polymorphonuclear leucocytes, and microglia activity, was diminished on the left side as compared with the right. At the 16-day period a slow rate of disappearance of the sponge on the

Fig. 2.—Bilateral wound; 10 mg. of hydrocortisone acetate suspension applied locally. Unhealed wound. Hematoxylin-phloxine-saffron; reduced about ⅓ from mag. × 25.



left side was obvious, and there was less fibroblastic proliferation. At 48 days there was a leptomeningocerebral cicatrix on the right side (Fig. 1), and on the left side the healing was delayed (Fig. 2), with remnants of the gelatin sponge still in the wound. The mobilization of microglia cells was diminished at all stages on the treated side. Pro-

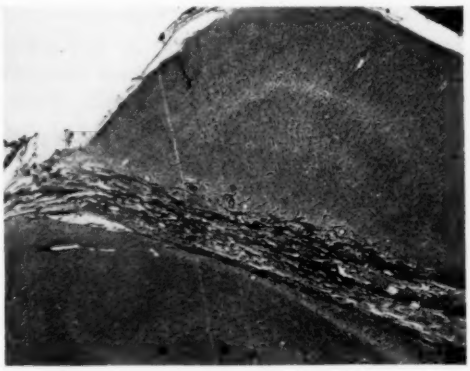


Fig. 3.—Bilateral wound; control side; 75 days. Reticulin of the meningocerebral cicatrix. Laidlaw's connective tissue stain; reduced about ⅓ from mag. × 25.

Fig. 4.—Bilateral wound; treated side; 75 days. Diminished meningocerebral cicatrix. Laidlaw's connective tissue stain; reduced about ⅓ from mag. × 25.

gressive changes of glia were the same on the two sides in the intermediate stages. In the 48-day wounds there was no increase in the number of glial cells on either side, and the glia on the treated side showed minimal hyperplasia and hypertrophy of the expansions.

2. *Long-Term Cats* (60, 75, and 90 days).—Cats with Bilateral Wounds (as in Group D): In this set of animals a leptomeningocerebral cicatrix was present on both sides. On the side of the local application of the hormone the scar was diminished (Figs. 3 and 4). Connective tissue was seen in the cicatrix in three layers: loose collagen and newly formed vessels in the center and a compact layer of fibroblasts to each side. These fibroblasts came from the arachnoid membrane of the superficial wound margins and went all the way to the depths of the wound. The limit between the brain and the connective tissue was sharp, and light intermingling of glial fibers with it was seen. In the 90-day wound there was an attempt of glial fibers to cross the wound from side to side. Hypertrophic changes of the glia were slightly more marked on the nontreated side. The zone immediately adjacent to the scar showed glia of normal appearance.

Microscopic examination of the pituitary showed normal cells in all specimens studied. The cortical neurones appeared normal. A direct action of the hormone on the nerve cells was not observed.

COMMENT

In the short-term group of animals we included unilateral and bilateral wounds. When they were compared, the unilateral control wounds and the control side of the bilateral wounds showed a similar pattern of healing, from the early inflammatory phase to the formation of a leptomeningocerebral cicatrix. The wounds that had local application of the hormone, 20 mg. of powder in the unilateral wounds and 10-mg. suspension in 0.9% saline with 0.9% benzyl alcohol in the treated side of the bilateral wounds, showed a delayed healing with a similar histological pattern, the depression being more marked when the powder form was applied in a higher dose. The suspension medium did not seem to influence the healing. The rates of healing of the control and the treated side of the bilateral wounds were different, each side following the same pattern of healing of the corresponding control and treated unilateral wounds. Finally, there was a possible minimal depression of healing when the hormone was given parenterally.

In the long-term group of animals, all with bilateral wounds, there was leptomeningocerebral cicatrix on both sides. A diminished scar with proliferation of fibroblasts in a less marked degree was seen on the side of the local application of the hormone.

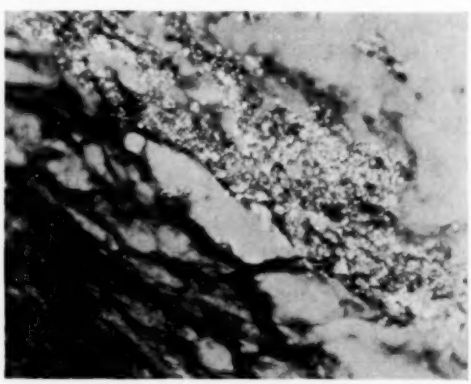
These experiments prove that hydrocortisone acetate applied locally, producing a high concentration of the hormone in the tissue, produces a delayed healing in wounds of the brain and diminishes the scar. The undesirable over-all action of high oral or parenteral doses does not take place.

Studies of the time of disappearance of the steroid crystals from the wound were not carried out. The hydrocortisone has a low solubility in cerebrospinal fluid and other body fluids,‖ which might indicate a slow absorption of the hormone from the wound. When hydrocortisone was applied in powder form, crystals were found in the 4-, 8-, and 16-day wounds (Fig. 5), confirming a slow absorption rate of the hormone from the wound.

In the bilateral wounds, diffusion of the hormone in the cerebrospinal fluid or its passage into the blood by absorption was not

‖ References 14 and 15.

Fig. 5.—Unilateral wound; 16 days; 20 mg. of hydrocortisone acetate powder applied locally. Crystals of hydrocortisone are still in place. Gold chloride-sublimate method of Cajal; polarized light; reduced about ⅓ from mag. × 350.



sufficient to affect the control wound. This wound is very similar to the unilateral control wound at the corresponding period of time.

Definite conclusions about the effects of parenteral administration of the hormone on the healing of wounds of the brain cannot be drawn from these experiments. Daily doses of a 10-mg. suspension of hydrocortisone acetate to cats with an average weight of 2.5 kg. did not produce changes in the adrenal glands. Nevertheless, the findings suggest an inhibitory effect in the healing of the wound, as judged by a less cellular cicatrix and a greater number of compound granular corpuscles in the wound of 48 days.

The process of repair was affected by the hormone in different ways. The early inflammatory reaction, judged by leucocytic infiltration and edema, was delayed. Microglial reaction appeared more intense at 16 days, while in the control wounds it was observed at 4 days. Fibroplasia occurs in the brain when the pia-arachnoid membrane and/or vessels have been severed. In the treated wounds it was suppressed in the early stages but appeared later, although in less pronounced degree. In the long-term group of wounds the difference in fibroblastic proliferation provides the objective measure of the degree of cicatrization. The glial elements are subsidiary, and the scar is dependent mainly on mesodermal elements. Phagocytosis, on which contradictory reports have been published in relation with cortisone,¶ was depressed. The gelatin sponge was used to show in part the phagocytic activity in the wound.

Depression of the process was evident when the sponge was still present in the treated unilateral and bilateral wounds at 48 days. Vascularization was also depressed, and nearly abolished in the early stages. This may be a fundamental factor in the healing of the brain. The contrary occurs in the cornea, where, although delayed healing is produced by the hormone, the vascular factor is considered irrelevant to the healing.[9] As a consequence of a depression in vascularization, the humoral mechanism of vasoastral symbiosis of Cajal has been altered, with a resultant indirect effect on the astrocyte cell. In the long-term wounds the difference in vascular proliferation and progressive changes of the glia is less marked, but they still persist as sequelae of an early depression. One may conclude, then, that the early inflammatory phenomena and the mesodermal tissues were affected by the local application of hydrocortisone.

Besides the several factors described above, the role of the astrocyte in the process of repair is to be considered. In the careful analysis of the mechanism of healing of wounds of the brain in cats made by Cajal,[18] he pointed out the importance of the astrocyte. In the present experiments this cell plays a secondary role in the healing process, as evidenced by the minimal regressive and progressive changes shown in the control and treated wounds and by the lack of active participation with the mesodermal elements in the healing process. A paper on the behavior of this cell will be published.

An analysis of the interrelation of the different cells and tissues affected by hydrocortisone and their role in the mechanisms of healing follows. It is generally accepted that cortisone acts on mesodermal, but not on epithelial, structures.# Microglia has been considered a representative of the reticuloendothelial system in the brain, and the depression of its function by the hormone, judged by a diminished mobilization in the early stages, a decreased number of abnormal forms, and the presence of normal cells in the intermediate stages at the wound margins, is further evidence of its mesodermal origin.

The depression of microglia is accompanied by diminished progressive changes in the glia. A humoral factor, depending on the normal activity of the microglia in the early stages and, later, on the connective tissue, is perhaps necessary to produce progressive changes in the glia. These changes

¶ References 16 and 17.

References 19 and 20.

were absent in the short-term treated wounds, and, although present in the long-term wounds, they were less marked than those on the control side. We have no evidence of a direct action of the hormone on the glial cells. The lack of gliosis is, then, an indirect effect. The early lack of vessel proliferation is not a primary factor in the lack of gliosis, as the astrocytes are attracted by the vessels after the astrocytes have been formed and migration is the last stage in the evolution of glial cells.

The results of this experiment show that fibroblastic proliferation is fundamental in the healing of the brain when the dura is intact and there are no dural adhesions (with the exception of the bilateral wounds of 75 days). Vascular proliferation has to be considered with fibroblastic proliferation. With early poor fibroblastic proliferation there was thinning of the vessels and no evidence of the vessels passing into the wound itself.

Differences in age of the animals, individual reactions to injury, and variability in wound production, as well as the difficulty in evaluation of the influence of the adrenocortical steroid in different animal species,[21] have to be considered, but the results of this experiment are consistent and in agreement with laboratory studies of the action of this steroid in tissue culture,[19] in experiments with animals of pure strain, and with multiple clinical observations in other tissues in man.

The results of this study suggest that if hydrocortisone is applied to wounds of the human brain, inflammation will be depressed, healing delayed, and the scar diminished.

SUMMARY

Local application of hydrocortisone acetate in powder and in saline suspension to incised stab wounds of the brain in cats produced delayed formation of a leptomeningocerebral cicatrix, and, as an end-result, a diminished meningocerebral cicatrix. The early inflammatory reaction, the phagocytic activity of the microglia, and the fibroblastic and vascular proliferation were depressed.

Mobilization of the microglial cells and participation of these cells in the process of phagocytosis is considered an important factor in the production of progressive changes in the astrocyte. The astrocyte has a secondary role in the process of healing of the brain, as evidenced by the presence of a mesodermal scar in the control and treated wounds, with light intermingling of glial fibers and minimal progressive changes in the astrocytes.

The results of this study suggest a possible clinical application of intrathecal or topical hydrocortisone in wounds of the brain or meninges when it is desired to diminish the cicatrix through delaying the repair process.

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Electroencephalography During Carotid Occlusion

Confusing Results in Thirty-Four Cases

JOHN M. POTTER, M.B., B.Chir., F.R.C.S.
and
F. M. TAYLOR, Oxford, England

During a recent period of approximately five years it was the custom in this department to take an electroencephalogram (EEG) before, during, and after the operation of carotid artery ligation in the neck, and this was done on 34 occasions. A period of trial occlusion of the artery by a rubber-covered clamp, for approximately 20 to 30 minutes immediately before ligation, was observed in each case; and neurological examinations were carried out in order to detect any signs of cerebral disturbance. Previously, in all but one case, carotid angiography, besides demonstrating the lesion to be treated, had shown the presence or absence of a free anastomosis across the anterior communicating artery when the opposite carotid had been compressed.

There has been a notion that this simultaneous EEG might in some subtle way give early warning (not evident clinically) of the occasional hemiplegia that still, despite the safeguards mentioned, follows this operation. Rogers'[1] original advocacy of this test was, however, based only on negative evidence from three cases, in none of which had there been any significant change in the EEG as a result of ligation of the common carotid artery.

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E. G. Fearnsides Scholar, University of Cambridge (Mr. Potter).

From the Department of Neurological Surgery, the Radcliffe Infirmary.

No large series of cases has, it seems, been carefully studied to assess the usefulness of this procedure, which is tedious for all concerned. During the preparation of this paper, however, Wise and associates[2] described 13 cases, in 4 of which an EEG was taken during the period of carotid occlusion, and their results were thought to indicate that the procedure is of limited value. Kidron[3] has reported 50 cases in which an EEG was taken during digital pressure to the "carotid vessels below the angle of the jaw." Others, e. g., Sweet and Bennett[4] and Hamby,[5] besides ourselves have been doubtful of the reliability of the digital method of occluding carotid arteries, even against Chassaignac's (carotid) tubercle. The criterion of occlusion in Kidron's investigation was absence of temporal pulsation, but this does not distinguish between common and external carotid compression. Furthermore, digital compression may, as noted in his paper, be distressing to the patient, and it is possible that carotid sinus mechanisms may be more readily evoked by this method than during the more precise surgical technique. These doubts must, therefore, be transferred in some measure to the results he obtained, which were none the less interesting: No change appeared in the records in 70% of the cases; in 20% minimal changes were seen, and in 10% only were there obvious changes, in the form of added slow-wave activity. The EEG before compression had little relation to the changes seen after compression.

From the additional information obtained in our series, we would say not only that its limitations are too great to warrant the trouble that the test entails, but that the capricious results which occur may confuse or mislead anyone not familiar with the wide variations that may be found. In particular, we have attempted—and without any notable

success—to correlate the EEG changes during the period of carotid occlusion with the patient's neurological state. We have also paid close attention to any predominant lateralization of the EEG changes, an aspect that does not seem to have been specially studied before.

MATERIAL AND METHODS

Material.—Thirty-four occlusions of carotid arteries in 30 patients have been carried out, with simultaneous EEG records. The common carotid artery was occluded, either temporarily or permanently, on 26 occasions and the internal carotid on 6. Three patients had first the common carotid tied, and this was followed one to two weeks later by internal carotid ligation. In one patient the external carotid was the second artery to be tied, as it was the more easily accessible, and in another patient the carotid artery occluded was not specified.

Aneurysms in the region of the termination of the internal carotid artery were the relevant lesions in 25 patients. Middle cerebral aneurysms were present in three, and a traumatic carotid-cavernous fistula, in one. In one man with subarachnoid hemorrhage (Case 26) an aneurysm at the origin of the posterior communicating artery had been suspected from a carotid arteriogram of poor quality. A second severe hemorrhage later resulted in common carotid ligation being performed, with some improvement; but two days later a fatal hemorrhage occurred from the aneurysm, which at autopsy proved to be after all at the basilar bifurcation.

Subarachnoid hemorrhage had occurred in all but two of these patients with aneurysms, usually several weeks before ligation was performed. Only five patients were significantly ill at the time of operation.

In 21 cases the lesion was right-sided, and in 9 it was on the left. The average age of the patients was 41 years, and the extremes of age, 18 and 65. Sixteen patients were women and 14 men.

Arteriographic evidence of a good anterior communicating anastomosis was obtained in 25 patients. In four it was absent or unsatisfactory, and in one case the test was not carried out.

The Operation.—The patients were usually given sufficient drugs to result in their experience of the operation being, retrospectively, one of agreeable surprise. Nevertheless, they were usually capable of accurate cooperation during the neurological examinations and were not showing persistent "sleep records" on the EEG. We have found the following combination of drugs satisfactory: Omnopon (a mixture of soluble hydrochlorides of opium alkaloids), ⅓ grain (20 mg.); scopolamine, 1/150 grain (0.4 mg.), and secobarbital (Seconal), 1½ grains (0.10 gm.), given three-quarters of an hour before operation. If the patient was still wakeful at the start of the operation, morphine, ⅙ or ¼ grain (10 or 15 mg.) was then added. The scalp electrodes were then applied and a preoperative EEG taken.

Local analgesia with 1% lidocaine (Xylocaine) hydrochloride has been employed latterly, but we have recently had reason to doubt the advisability of using epinephrine in addition to this where there is a recently ruptured aneurysm, particularly if there is already a tendency to hypertension.

The common (or internal) carotid was exposed in a conventional manner through a "half-collar" incision in a skin crease, and a rubber-covered Crile clamp applied. An EEG was taken immediately and at short intervals, and clinical tests were carried out briefly between times, and searchingly at the end of half an hour. If by that time no serious and consistent EEG or clinical change had occurred, the artery was ligated in continuity with No. 4 twisted nonabsorbable surgical (silk) sutures at two points approximately 1 cm. apart. The ligatures were left with their ends long, in case their rapid removal should be desired subsequently, for we have not felt it wise to take the irrevocable step of dividing the artery, as recommended by Rogers,[6] but one which seems unpopular with most other authors, e. g., Holman and associates,[7] Hamby,[5] and Brackett.[8] After closure of the wound, a further EEG was taken.

The EEG Technique.—An Ediswan six-channel machine was used in the majority of cases, but four early records were taken on a Grass three-channel instrument. Electrodes (the routine silver-silver chloride type) were placed over the frontal, temporal, and parietal areas on both sides. The operations were performed in the ward surgical dressing room, next to the EEG room, and the leads passed through the adjoining doors. In all cases a short recording was made immediately before the incision. In this way a base line was established, particularly to assess the effects of the "premedication." In many cases there were also earlier records for comparison.

The electrodes remained in position under sterile towels during the operation, but were accessible, for occasionally trouble was caused by their becoming displaced. Immediately the carotid was clamped, recording was carried on for two to three minutes, after which further short records were taken at approximately five-minute intervals. This was done also after ligation, and another record was taken at the end of the operation. Most cases had further postoperative records taken at varying intervals.

Clinical Signs.—All patients received a careful neurological examination before operation. Any

changes occurring during or after carotid occlusion were then noted in relation to the preoperative state. These changes have been classified as immediate (those occurring during the period of trial occlusion) and delayed. In each of these groups any change in the physical signs has been noted as slight or severe.

Electroencephalographic Changes.—These have been more difficult to classify, and no method seems wholly satisfactory if results are to be recorded concisely and clearly. Ours has been an arbitrary system which attempts to grade the degree of "deterioration" of a given record:

Grade 1: A normal record

Grade 2: Minor disturbances, such as those of the alpha rhythm

Grade 3: More marked change, such as the occurrence of theta activity as a prominent feature

Grade 4: Still more marked deterioration, with delta waves especially

Grade 5: Flattening of the record, with "silence" at the extreme end of the grade

or to the circumstances of the particular case. The report of the original observer has then been referred to, and any special circumstances of the case, such as artifacts and excessive drowsiness of the patient, have been taken into account. In most cases a third examiner has given an independent opinion.

RESULTS

In Table 1 those patients showing an increased neurological defect following carotid occlusion are considered primarily against any concomitant EEG changes. (It has not been found useful to tabulate common and internal carotid occlusions separately, owing to the small number of the latter.)

Of the eight cases which presented immediately a mild clinical defect, only five showed a corresponding slight deterioration of the EEG; and of the latter, two showed no lateralization of the change, in two the change was ipsilateral, and in one, contralateral. Two cases showed no EEG change at all, and in one the record seemed to improve a little (there was less delta activity), in spite of the clinical abnormality.

TABLE 1.—*Clinical Defects Compared with Electroencephalographic Changes Following Carotid Occlusion*

Cases Showing Clinical Deterioration After Carotid Occlusion	EEG Changes				Lateralization of EEG Deterioration			Good "Cross Circulation"
	Nil	Slight Improvement	Slight Deterioration	Marked Deterioration	Nil	Ipsilateral	Contralateral	
Immediate								
Mild 8	2	1	5	..	2	2	1	7
Severe 1	..	..	..	1	..	1	..	1
Delayed								
Mild 5	1	1	3	..	2	..	1	4
Severe 2	..	..	2	..	1	..	1	1

In some respects our task has been made easier by the occurrence of a fairly constant type of deterioration in these records—one of progressive frequency slowing, and a tendency toward decreasing amplitude in the late stages.

All EEG changes that have occurred during or after carotid occlusion have been noted in relation to the preoperative records; and such changes as have taken place have generally shown either slight deterioration or marked deterioration, but in a few there has been a slight improvement in the record. (By "improvement" we mean merely that a patient's record showed less disturbance as compared with that taken before carotid occlusion, and was therefore upgraded in our system.) As stated earlier, we have given particular attention to any lateralization that has occurred in those records showing changes.

In assessing the EEG records, we have endeavored to guard against any bias. We have examined the tracings carefully, as far as possible without reference to the original report on them

The one case, a woman of 65 (Case 25), in which severe hemiplegic signs developed immediately after carotid occlusion, showed also marked deterioration of the EEG on the side of the occlusion, and ligation was not performed. She had had a primary subarachnoid hemorrhage from an aneurysm at the origin of the posterior communicating artery the previous day, and she died of another hemorrhage four days later, the case thereby illustrating the complexity of the therapeutic problem.

Five cases showed mild delayed clinical abnormalities, and three of these had slight

EEG deterioration, one contralateral and the others not lateralized. Another of these cases showed no EEG change, and one showed some improvement in the record—again less delta activity, and again despite the clinical signs.

Neither of the two cases developing severe delayed hemiplegia showed more than slight EEG deterioration at the time of occlusion. In one, a man aged 49 (Case 30), who was probably still bleeding from his aneurysm, this change was not lateralized; and, although a slight left hemiparesis was apparent immediately after the ligation, it had cleared the next day, but recurred and became complete three days later. After a year, he has made an incomplete recovery, but can walk. In the other (Case 20) a man of 58 with an unruptured aneurysm near the origin of the right posterior communicating artery was quite well at the time of right carotid ligation, when a slight EEG deterioration was referable to the contralateral cerebral hemisphere. A profound hemiplegia developed eight hours later, but he finally recovered almost completely. Both these cases, however, showed some ipsilateral deterioration in the EEG by the time the hemiplegia had developed; but there had been no reason to predict the complication, for the slight EEG changes had been no more than those seen in cases showing no clinical defect (Table 2).

Table 2 is a reciprocal of the first, and in it the EEG changes, with their lateralization, if any, are shown against the clinical state. Three of the 10 patients showing no EEG changes developed mild neurological abnormalities, 2 immediately and 1 delayed. Two of the seven cases in which there was slight EEG improvement showed the development of mild abnormal signs, and these have been mentioned. The other five already had grossly abnormal EEG's, and the improvement was chiefly that of greater stability and of decrease in delta activity. But 7 of the 15 patients with slight EEG deterioration showed no clinical change, and the lateralization of this deterioration was haphazard. Of the two cases showing marked EEG deterioration, one developed an immediate, severe hemiplegia, and the other showed no neurological abnormality at any time.

In both Tables the number of cases passing the "cross-circulation" test is shown. Table 3 contains a synopsis of the relevant features of the 30 cases in this series.

TABLE 2.—*Electroencephalographic Changes VersusClinical Deterioration Following Carotid Occlusion*

EEG Changes		Lateralization of Change			Clinical Deterioration					Good "Cross Circulation"
						Immediate		Delayed		
		Nil	Ipsilateral	Contralateral	Nil	Mild	Severe	Mild	Severe	
No change	10	..	..	..	7	2	..	1	..	6
Slight improvement	7	3	3	1	5	1	..	1	..	7
Slight deterioration	15*	3	7	5	7	5	..	3	2	14
Marked deterioration	2	1	1	..	1	..	1	.	..	2

* Two of these showed both immediate and delayed clinical changes.

DEATHS

Although the four deaths occurring in this series have no strict relevance to the main problem under consideration, they are of general and practical interest. A youth aged 20 (Case 21) with a right internal carotid aneurysm was already stuporous and tetraplegic (the left side being the more affected) at the time of ligation, as he had had a subarachnoid hemorrhage (his second) four days earlier. There had also been subdural bleeding, necessitating a subtemporal decompression. His EEG, already grossly abnormal (Grade 4 to 5), improved a little after ligation, but there was no consistent clinical improvement and he died five weeks later. At autopsy gross infarction of most of the right cerebral hemisphere was found, but the clinical evidence suggested that this may have anteceded the carotid ligation.

TABLE 3.—*Summary of Relevant Features of Thirty Cases with Carotid Occlusion*

Case No.	Sex	Age, Yr.	Lesion	Artery Occluded †	Anterior Anastomosis Test	EEG Grading: Pre-operative	EEG Grading: During Occlusion	EEG Grading: Post-operative	Lateralization of Change	Clinical Changes
1	F	42	Right internal carotid aneurysm *	R.C.C.	Nil	3	3	3	.....	Subjective "burning" of left side of body the following day
2	M	45	Right internal carotid aneurysm	(*a*) R.C.C. (*b*) R.I.C.	Yes	(*a*) 2-3 (*b*) 2	2 3	... ...	Nil Nil	Nil Transient minimal left hemiparesis 2 days later
3	F	29	Right internal carotid aneurysm	R.C.C.	Not satisfactory	3-4	3-4	3-4	.....	Nil
4	M	50	Left internal carotid aneurysm	(*a*) L.C.C. (*b*) L.I.C.	Yes	(*a*) 2-3 (*b*) 3-4	3-4 4	3 ...	Ipsilateral Ipsilateral	Nil
5	F	35	Right carotid cavernous fistula	R.C.C.	Yes	4	3-4	3-4	Ipsilateral	Nil
6	M	49	Right internal carotid aneurysm	R.C.C.	Yes	3	3-4	3	Contralateral	Slight weakness of right arm the next day only
7	M	47	Right middle cerebral aneurysm	R.C.C.	Yes	2	2-3	2	Contralateral	Nil (fatal hemorrhage 5 days later)
8	F	40	Right internal carotid aneurysm	R.C.C.	Yes	3-4	4	3-4	Contralateral	Transient loss of joint position sense in left hand during occlusion
9	F	47	Right internal carotid aneurysm	(*a*) R.C.C. (*b*) R.E.C.	Yes	(*a*) 3 (*b*) 3	3 3	3 3	....	Transient left Babinski sign and defective joint sense in left fingers and toes during occlusion Nil
10	F	28	Left internal carotid aneurysm	L.C.C.	Yes	3	3	3	.....	Nil
11	M	45	Left internal carotid aneurysm	L.C.C.	Yes	3	3	3	.....	Minimal right hemiparesis and dysphasia, lasting a week
12	F	42	Right and left internal carotid aneurysms	R.C.C.	Yes	3-4	3-4 (less marked)	3-4	Ipsilateral	Nil
13	F	44	Left internal carotid aneurysm	L.C.C.	Yes	1	3	1-2	Nil	Nil
14	M	37	Right internal carotid aneurysm	R.C.C.	Yes	4	4-3	2-3	Contralateral	Nil
15	F	51	Right internal carotid aneurysm	R.C.C.	Yes	3	3-4	3-4	Ipsilateral	Slight weakness of left hand; left Babinski sign, followed by right; all transient and during occlusion
16	F	29	Right internal carotid aneurysm	R.I.C.	Yes	3	3-4	2	Ipsilateral	Nil
17	M	18	Right internal carotid aneurysm	R.C.C.	Yes	4	4	2	Nil	Nil

Case No.	Sex	Age, Yr.	Lesion	Artery Occluded †	Anterior Anastomosis Test	EEG Grading			Lateralization of Change	Clinical Changes
						Pre-operative	During Occlusion	Post-operative		
18	F	40	Right internal carotid aneurysm	R.C.C.	Yes	3-4	4	3-4	Nil	Transient weakness of right wrist during occlusion; transient paresthesia in left hand the next day
19	M	48	Left internal carotid aneurysm	L.C.C.	Yes	3	3	3	.....	Nil
20	M	58	Right internal carotid aneurysm	R.I.C.	Yes	2-3	3-4	2-3	Contralateral	Profound left hemiplegia developed after 8 hr.; improvement within 24 hr.; almost complete recovery
21	M	20	Right internal carotid aneurysm	R.C.C.	Yes	4-5	4	4	Ipsilateral	No obvious change, but patient already stuporous and tetraplegic (died 5 wk. later)
22	F	42	Left internal carotid aneurysm	L.I.C.	Nil	3	3	3	.....	Nil
23	F	47	Left internal carotid aneurysm	L.C.C.	Yes	4	4 (slightly improved)	3-4	Nil	Transient weakness of right leg during occlusion
24	F	31	Left middle cerebral aneurysm	L.C.	Yes	3	3	3	.....	Nil
25	F	65	Right internal carotid aneurysm	R.C.C.	Yes	2-3	4	3-4	Ipsilateral	Left hemiplegia occurred after 20 min. of occlusion; complete recovery after removal of clamp; no ligation (death from further hemorrhage 4 days later)
26	M	42	Basilar bifurcation aneurysm	R.C.C.	Not tested	...	4	3	.....	No change but patient already stuporous; died 2 days later
27	M	57	Left internal carotid aneurysm	L.C.C.	Yes	4	4-5	4-5	Ipsilateral	Nil
28	M	45	Right middle cerebral aneurysm	R.C.C.	Yes	2-3	3	2	Contralateral	Nil
29	F	51	Right internal carotid aneurysm	(*a*) R.C.C.	Yes	(*a*) 4	4 (improved)	3	Ipsilateral	Slight increase in left arm weakness after 4 days
				(*b*) R.I.C.		(*b*) 3-4	4	3-4	Ipsilateral	Left Babinski sign during occlusion
30	M	49	Right internal carotid aneurysm	R.C.C.	Nil	3	4	3	Nil	Slight left hemiparesis at occlusion, improving next day; complete left hemiplegia on 3d day; gradual but incomplete recovery

* Internal carotid aneurysm includes, for convenience, all aneurysms occurring around the termination of that artery.

† C.C. means common carotid; I.C., internal carotid; E.C., external carotid.

A man of 47 (Case 7) had a subarachnoid hemorrhage from the right middle cerebral aneurysm. Two months later a right common carotid artery ligation was performed, at which time he was quite well. The ligation resulted in a slight EEG deterioration referable to the contralateral (left) cerebral hemisphere, but there were no abnormal clinical signs. Five days later he had a fatal hemorrhage into his right frontal lobe.

Case 26 has already been referred to as one in which the patient died of a ruptured basilar aneurysm two days after a right common carotid ligation, performed in the mistaken belief that there was an aneurysm of the right posterior communicating artery. At the time of occlusion he was stuporous and had a Grade 4 EEG, which was rather worse on the left side. This improved to Grade 3, along with the improvement in his level of consciousness the following day.

Case 25, the woman of 65 who was intolerant of right common carotid occlusion, has also been described already.

COMMENT

It is clear that, in the majority of these cases, cutting off the blood supply from one carotid artery was of little moment to the brain; and our series would have been of greater interest and value had there been more cases showing complications. Also, the shortcomings, from the purely statistical aspect, of such small numbers are fully appreciated. There is perhaps a tendency still, despite evidence from papers such as those of Schorstein [9] and of Brackett,[8] not to tie carotid arteries of elderly patients. It is generally agreed, however, that the patient who is acutely ill, with recent or persisting subarachnoid hemorrhage, is more certainly a poor risk. From our figures, it seems that there has also been some reluctance to ligate when the lesion was on the left side. All this must be borne in mind when we say that this is otherwise an unselected series of all patients deemed to require the operation in a recent five-year period.

We agree fully with the findings of Wise and associates [2] that "slight to marked electrical abnormalities may appear following carotid ligation without clinical evidence of cerebral damage," and vice versa. Further, there may be failure of the EEG to "predict" the occurrence of a delayed hemiplegia—an observation due also to Elvidge and Feindel.[10] Wise and associates paid attention to "slight focal changes consisting of homologous differences of potential, wave form, and synchrony, as well as wave frequency," but apparently without much useful result; and we have been unable, in this series, to attribute any significance to such changes. We have been anxious to avoid sleep records, although Epstein and Lennox [11] found more abnormality in the sleep records of dogs with experimental middle cerebral artery occlusion than in the waking records. Moreover, only the sleep records continued to show abnormality after about eight days.

The lateralization of the EEG deterioration is interesting; and it is the change from the preoperative record to the record taken during and after occlusion that has been considered, for often some degree of abnormality has already been present. It seems likely that both cerebral hemispheres are to some extent influenced by a single carotid occlusion, and in several cases no lateralization was seen. It is difficult to find a satisfactory explanation as to why it should have been the contralateral cerebral hemisphere that showed the greater change in more than half the cases which had both lateralized EEG change and clinical deterioration and in a third of all cases showing EEG changes. We realize that there are possible grounds on which our results might be criticized, the most important being that common to all EEG work, namely, the observer error. We have, however, reexamined the tracings with particular reference to possible artifacts, and still feel that these observations should be placed on record. We will not comment further on this point, except to note here also that in three cases clinical changes occurred in the limbs on the side of the carotid occlusion, although in one case signs were present on both sides.

The accompanying EEG changes in these three cases were, however, inconsistent: In one they were predominantly ipsilateral; in another they were contralateral, and in the third there was no specific lateralization.

Of the other, more practical, points that emerge, one is that mild, immediate or delayed clinical abnormalities may occur that are not of serious import. These may or may not be associated with EEG changes; and, likewise, slight deterioration in the EEG was as often as not unaccompanied by clinical abnormality. Meyer and associates [12] have recently found indirect evidence that EEG changes do not occur until the "oxygen availability" to the brain is reduced by more than 20%, when decreased amplitude and slowing are seen. This was the pattern of change found most constantly, though not invariably, in the records in this series, and noted also by some other workers. The useful review of the literature by Wise and associates [2] reveals this, but otherwise it seems that there has been no great unanimity of opinion concerning the EEG changes in what is assumed to be cerebral anoxia, produced in various ways. Moreover, the occurrence of a relatively normal or unchanged EEG in the presence of an overt and recent hemiplegia has puzzled others (e. g., Elvidge and Feindel [10]) besides ourselves.

It must be said, however, that the two severe delayed hemiplegias occurring in this series were both in patients in the group which had shown slight EEG deterioration during carotid occlusion; but against these, and seven patients showing also mild (five immediate and two delayed) clinical abnormalities, there were seven cases in this group who had no clinical disturbance whatever. An explanation may be that one of the hemiplegics (Case 20) was 58 years of age and had thickened peripheral arteries (but a normal blood pressure), and the other (Case 30) was already seriously ill, and probably still bleeding, after a subarachnoid hemorrhage five days earlier; he had shown no anterior communicating anastomosis at angiography. If a mild EEG deterioration is to be taken as a serious warning, then many patients will be denied carotid ligation who would in fact tolerate it comfortably.

The anterior communicating anastomosis ("cross-circulation") test has been without significance in other cases in this series, there being three where the anastomosis was apparently absent or unsatisfactory. One showed no EEG change, but mild, delayed, and transient clinical abnormalities; and the other two showed neither EEG nor clinical changes. Conversely, other cases showing clinical and EEG abnormalities had a good anterior communicating anastomosis. It seems likely that this test contributes as little as the EEG toward solving problems associated with carotid ligation, for, after all, the anterior communicating artery is but one of the three main anastomotic channels remaining to supply the anterior half of the circle of Willis on the side of a ligated common carotid artery. Further, it is not the only place where the collateral circulation may be deficient, so that bilateral carotid angiography is still desirable in order to exclude the presence of other anomalies of the circulus arteriosus, as well as other aneurysms.

In dealing with this whole subject, we are nowadays more aware of the principle, foreshadowed in part by Schorstein,[9] of "acute cerebral circulatory (or vascular) insufficiency" (Denny-Brown [11]; Corday and associates [14]), and pay more attention to such general circulatory factors as the maintenance of an adequate blood pressure. We have examples of several patients in whom the hypotension of a coronary artery occlusion has apparently precipitated an episode of insufficiency of the cerebral circulation, and this exciting cause seems liable to be overlooked in the face of the more dramatic neurological picture, as in one case with a lateral bulbar syndrome we have observed. One example of this occurrence, especially relevant to the matter in hand, was that of a woman of 55, who is not in the present series of cases. A complete left third nerve palsy indicated the site of the aneurysm, and a left common carotid artery ligation was performed in the presence of a severe, second subarachnoid hemorrhage, which had oc-

curred before angiography could be done. During the next two hours she developed a complete right hemiplegia with aphasia; so the ligatures were removed two and one-half hours after the ligation, with immediate and dramatic recovery of the paralysis. After continuing well for five days, she had a coronary thrombosis with a fall in blood pressure, but without evidence of further intracranial hemorrhage; and there was a return of the hemiplegia and aphasia, which have persisted.

Thus, despite the attention that the problems of carotid ligation have received from numerous recent publications, and apart from an increased awareness of the general circulatory factors already discussed, we are back where we were before the advent of the anterior anastomosis test and the EEG, and are relying on some form of preoperative occlusion test and rejecting cases in which, clinical judgment tells, the risks of ligation appear to outweigh those of the lesion to be treated. It may be that measurement of the intracarotid pressure before and after occlusion (Sweet and associates * Johnson [16]) will prove a useful investigation. Yet the immediate hemiplegia needs no special tests for its recognition during trial occlusion, and a partial ligation may then be feasible. It is the prediction of the delayed hemiplegia that is likely to be a greater problem.

SUMMARY

Carotid arteries have been occluded by a clamp on 34 occasions as a test of the effects of ligation. Simultaneous electroencephalographic tracings were made, and clinical neurological examination was carried out in all cases.

The EEG is unhelpful in solving the problems associated with carotid ligation. It may show "deterioration" which is unaccompanied by clinical neurological changes, and vice versa. It does not necessarily "predict" a delayed hemiplegia.

The most constant type of deterioration was one of a decrease both in the frequency and in the amplitude of the waves. The record may even show some improvement.

When there was EEG deterioration during carotid occlusion, it was referable particularly to the contralateral cerebral hemisphere in a third of the cases.

Mild clinical abnormalities, either immediate or delayed, may occur during carotid occlusion, but are not necessarily of serious import.

The angiographic anterior anastomosis ("cross-circulation") test has not proved useful, either.

Relative contraindications to carotid ligation should be assessed by attention to the patients' preoperative condition, particularly to clinical evaluation of the cardiovascular system and to carotid arteriography, as well as to the presence of recent or continued subarachnoid hemorrhage. Contraindication is present only when gross hemiplegic signs develop during a trial period of carotid occlusion, when a partial ligation may be feasible.

Miss F. Boselli assisted with many of the electroencephalograms.

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Cerebrospinal Fluid Inorganic Phosphorus in Normal and Pathologic Conditions

ABRAHAM FRIEDMAN, M.D., Haifa, Israel
and
ABRAHAM LEVINSON, M.D., Chicago

Phosphorus is the most important mineral constituent of nerve tissue, of both the white matter and the gray matter.[1] In view of this, it is conceivable that histologic changes in the brain substance might be reflected by a change in the inorganic phosphorus level of the cerebrospinal fluid. It is no wonder, therefore, that the study of the inorganic phosphorus of cerebrospinal fluid, in normal and in pathologic conditions of the central nervous system, has aroused considerable interest. In spite of this, however, this chapter is far from closed.

The results of the various studies on this subject seem to be fairly consistent as regards the normal range of cerebrospinal fluid inorganic phosphorus. Elevated values have also been consistently reported in a number of pathologic conditions. In other pathologic conditions, however, the results of various investigators are rather conflicting. Nor has unanimity been reached on the subject of the origin of the elevated cerebrospinal fluid phosphorus in certain pathologic conditions, and its clinical significance.

In this paper we wish to report upon the results of a study of the inorganic phosphorus content of the cerebrospinal fluid under normal and in pathologic conditions. We should also like to discuss the mechanism and the clinical significance of the pathologic changes in the phosphorus level of the cerebrospinal fluid.

REVIEW OF LITERATURE

The literature on cerebrospinal fluid inorganic phosphorus has been reviewed by Levinson,[2] Kafka,[3] and Katzenelbogen.[4] Of the various papers reviewed by these authors, the most important, and the one deserving special mention, is that of Cohen.[5] He carried out the most extensive study to date of cerebrospinal fluid inorganic phosphorus and found the normal values to range from 1.25 to 2.0 mg. per 100 cc., with an average of 1.64 mg. per 100 cc. In pathologic conditions, Cohen found the cerebrospinal fluid phosphorus to be elevated in tuberculous meningitis, meningococcic meningitis, and acute syphilitic meningitis.

Following the reviews mentioned, the number of papers dealing with the problem of cerebrospinal fluid phosphorus that have appeared in the literature is comparatively small.

Cohn and associates [6] studied cerebrospinal fluid phosphorus in normal and in pathologic conditions and found a normal range of 1.0 to 1.5 mg. per 100 cc., with an average of 1.4 mg. per 100 cc. They found elevated cerebrospinal fluid phosphorus values in tuberculous meningitis, purulent meningitis, hydrocephalus, and brain tumor.

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From the Dr. Julian D. Levinson Research Foundation; the Children's Division of the Cook County Hospital, and the Hektoen Institute for Medical Research.

Research Fellow in Pediatric Neurology at the Dr. Julian D. Levinson Research Foundation and at the Children's Division of the Cook County Hospital (Dr. Friedman; permanent address: Rambam Hospital, Haifa, Israel). Director of the Dr. Julian D. Levinson Research Foundation and Chief of Staff and Head of the Neuropsychiatric Service of the Children's Division of the Cook County Hospital (Dr. Levinson).

Giunti and Rottini [7] found normal cerebrospinal fluid phosphorus values between 1.4 and 1.9 mg. per 100 cc. In pathologic conditions, namely, tuberculous meningitis, dementia paralytica, aseptic meningitis, cerebral thrombosis, meningoencephalomyelitis, and poliomyelitis, they found the cerebrospinal fluid phosphorus to be within the normal range, with the exception of tuberculous meningitis, in which the cerebrospinal fluid phosphorus was actually lower than normal.

Garsche and Souchon [8] studied cerebrospinal fluid phosphorus in tuberculous meningitis under streptomycin therapy. They found it to be raised initially. It decreased, progressively, to normal when the results of therapy were favorable, but increased markedly when the meningitis became chronic, particularly during the development of hydrocephalus.

Ragazzini [9] also studied the cerebrospinal fluid phosphorus in the course of tuberculous meningitis and found it increased.

Odessky and associates * studied extensively the cerebrospinal fluid phosphorus in the normal and in pathologic conditions, mainly viral in nature. They [10] found the normal to vary from 0.9 to 2.0 mg. per 100 cc., with an average of 1.4 mg. per 100 cc. In pathologic conditions they found the cerebrospinal fluid phosphorus to be elevated in measles encephalitis,[11] mumps meningoencephalitis,[12] poliomyelitis,[13] varicella encephalitis,[14] and influenza meningitis.[14]

* References 10 to 14.

MATERIAL

Our material consists of 216 specimens of cerebrospinal fluid on which inorganic phosphorus determinations were done. In 194 of the cases, phosphorus determinations were also done on blood specimens which were obtained simultaneously with the cerebrospinal fluid. The complete studies, carried out on both the cerebrospinal fluid and the blood serum, included, in addition to the inorganic phosphorus, protein, glucose, sodium, potassium, and chloride determinations. The cerebrospinal fluid specimens were also examined for cell count and type of cells, Pandy and Kahn reactions, and cultures.

Of the 216 cerebrospinal fluid specimens studied, 149 were obtained from 106 children and 67 specimens from 66 adults. The children studied were all hospitalized patients of the Children's Division of the Cook County Hospital. The adults were inpatients of the Cook County Hospital and Cook County Psychopathic Hospital. All specimens were drawn for diagnostic purposes, with the exception of one group, in which the cerebrospinal fluid specimens were removed prior to the administration of spinal anesthesia for surgery.

Table 1 shows the distribution of the material according to the diagnosis of the cases studied.

Group A comprises 14 specimens from children with meningism accompanying acute infections. The basic acute infection consisted of bronchopneumonia, in six cases; upper respiratory infection, in five, and otitis media, in four. In all cases the

TABLE 1.—*Distribution of Material Studied According to Diagnosis*

Group	Diagnosis	No. of Determinations of Inorganic Phosphorus in Cerebrospinal Fluid			No. of Simultaneous Determinations of Inorganic Phosphorus in Blood Serum*			No. of Patients Studied*		
		T	A	C	T	A	C	T	A	C
A	Meningism	14	..	14	13	..	13	14	..	14
B	Febrile convulsions	8	..	8	8	..	8	8	..	8
C	Pulmonary and miliary tuberculosis	11	1	10	11	1	10	9	1	8
D	Mental retardation	24	..	24	22	..	22	21	..	21
E	Epilepsy	13	9	4	10	9	1	12	8	4
F	Tuberculous meningitis	49	..	49	43	..	43	18	..	18
G	Purulent meningitis	14	..	14	11	..	11	9	..	9
H	Poliomyelitis	13	..	13	13	..	13	13	1	12
I	Acute encephalitis	6	..	6	6	..	6	5	..	5
J	C. N. S. syphilis	5	3	2	4	2	2	5	3	2
K	C. N. S. manifestations of chronic alcoholism	14	14	..	13	13	..	14	14	..
L	C. N. S. arteriosclerosis	6	6	..	4	4	..	6	6	..
M	Miscellaneous neurologic conditions	23	19	4	20	17	3	22	18	4
N	Miscellaneous non-neurologic conditions	16	15	1	16	15	1	16	15	1
	Total	216	67	149	194	61	133	172	66	106

* T indicates total; A, adult; C, child.

cerebrospinal fluid was normal in every respect as judged by standard criteria of normality.

Group B consists of 8 specimens from children with febrile convulsions, accompanying, mainly, upper respiratory infections. In all cases of this group the cerebrospinal fluid was normal in every respect.

Group C comprises 11 specimens from patients with pulmonary tuberculosis (6 specimens) or miliary tuberculosis (5 specimens). The cerebrospinal fluid was drawn in these cases for the purpose of excluding the possibility of incipient tuberculous meningitis. All specimens were normal by standard criteria of normality.

Group D consists of 24 specimens from patients with mental retardation. The cause of the retardation varied. Some cases were genetic in origin, while most others were acquired as sequelae of prematurity, cerebral birth injury, postnatal meningoencephalitis, or other conditions. All these patients were studied not in the acute stage of their basic neurologic disease but after a prolonged period following the brain damage. In all cases o fthis group the cerebrospinal fluid specimens were entirely normal.

Group E comprises 13 specimens from patients with epilepsy. The epilepsy was idiopathic in eight cases and acquired, as a result of birth injury, head trauma, etc., in the others. The cerebrospinal fluid in all these cases was normal in every respect.

Group F consists of 49 specimens from patients with tuberculous meningitis. The diagnosis was established on clinical, biochemical, and bacteriological grounds. All cerebrospinal fluid specimens showed a moderate lymphocytic leucocytosis, a positive Pandy test, and a raised protein and a lowered sugar content.

Group G consists of 14 specimens from patients with acute purulent meningitis. The bacterial agent recovered from the cerebrospinal fluid was Hemophilus influenzae in 11 specimens, Meningococcus in 2, and Staphylococcus in 1. All cerebrospinal fluid specimens showed a marked polymorphonuclear leucocytosis, a positive Pandy test, and a high protein and a low sugar content.

Group H consists of 13 specimens from patients in the acute stage of paralytic poliomyelitis. The cerebrospinal fluid specimens showed a mild to moderate lymphocytic leucocytosis, a positive Pandy reaction, a slightly elevated protein in most cases, and a normal sugar content.

Group I consists of six specimens from patients with acute encephalitis, of undetermined etiology. The cerebrospinal fluid showed an increased number of cells, a positive Pandy reaction, and a normal sugar and a raised protein content.

Group J consists of five specimens from patients with neurosyphilis. Two of the 5 patients were children, aged 5 and 9 years old, respectively, with central nervous system manifestations of congenital syphilis. The other three were adults. The cerebrospinal fluid in these cases showed a positive Wassermann or Kahn test and/or a positive colloidal gold test, as well as a positive Pandy test and a raised cell count.

Group K consists of 14 specimens from patients with neurologic manifestations of chronic alcoholism. These consisted of neuritis, in four cases; delirium tremens, in five, and epileptic seizures, in five. All cerebrospinal fluid specimens of this group were normal by standard criteria of normality.

Group L consists of six specimens from patients with clinical evidence of cerebral arteriosclerosis. The cerebrospinal fluid showed no cells, normal sugar, a positive Pandy reaction, and a slightly elevated protein level in five of the six patients.

Group M consists of 23 specimens from patients with miscellaneous neurologic conditions. This group, with their specific diagnosis, is presented in Table 2, which also shows the results of the cerebrobrospinal fluid and blood serum examinations in each case.

Group N consists of 16 specimens from patients with miscellaneous non-neurologic conditions. The cases of this group were patients in which the cerebrospinal fluid was removed prior to the administration of a spinal anesthetic for surgery. This group, with the specific diagnoses, is presented in Table 3, which also showed the results of the cerebrospinal fluid and blood serum examinations in each case.

METHODS

The technique employed for the inorganic phosphorus determination was the Fiske and Subbarow method, as modified for the photoelectric colorimeter by Hoffman.[15] The other laboratory procedures were performed according to standard methods.

All the laboratory examinations were carried out at the laboratories of the Hektoen Institute for Medical Research.

RESULTS

It would be very cumbersome and space-consuming to present in this paper, which deals with cerebrospinal fluid phosphorus only, the complete results of the analysis of all the cerebrospinal fluid and blood serum specimens that were examined. With the exception of the last two groups, we shall, therefore, limit ourselves to the presentation of the data pertaining to inorganic phosphorus only. This information has already been supplemented, with general data on the cerebro-

TABLE 2 (Group M).—*Patients with Miscellaneous Neurologic Disorders*

Patient No.	Diagnosis	Age, Yr.	Kahn Test	Cells	Pandy Test	Protein		Sugar, Mg./100 Cc.		Phosphorus Mg./100 Cc.	
						Serum, Gm./100 Cc.	CSF, Mg./100 Cc.	Serum	CSF	Serum	CSF
1	Cerebral hemorrhage	55	—	0	—	7.50	16	36	54	4.8	1.7
2	Cerebral hemorrhage	50	—	0	—	6.75	16	128	67	3.0	1.6
3	Cerebral embolism	47	..	1	—	6.10	16	160	80	3.3	1.6
4	Cerebral thrombosis	47	—	0	2+	6.55	86	72	48	3.0	1.7
5	Subdural hematoma	6/52	—	0	—	5.38	..	40	40	5.6	1.3
6	Cerebral birth injury	2/12	—	0	+	6.16	40	88	60	3.8	2.2
7	Brain tumor	33	—	0	—	7.32	31	124	112	3.1	1.7
8	Brain abscess	2	—	15	2+	....	45	..	81	...	1.9
9	Acute cerebellar ataxia	11	—	63	—	8.38	21	123	64	5.1	1.6
10	Hysteria	24	—	0	—	7.38	37	80	62	4.3	1.8
11	Pernicious anemia with S. C. D.*	41	—	2	—	6.85	23	80	58	2.8	1.8
12	Cord tumor	62	—	0	4+	7.23	292	84	56	4.1	3.8
13	Compression myelitis	44	—	0	4+	7.0	108	88	44	4.8	2.5
14	Guillain-Barré syndrome	52	—	0	4+	...	1052	80	48	...	1.5
15	Guillain-Barré syndrome	52	—	0	4+	6.75	896	80	36	4.3	2.7
16	Polyneuritis	16	—	0	—	7.55	14	62	62	4.6	1.7
17	Amyotrophic lat. sclerosis	53	—	0	—	....	33	88	54	...	1.7
18	Amyotrophic lat. sclerosis	54	—	0	3+	6.9	194	80	62	2.4	2.2
19	Amyotrophic lat. sclerosis	61	—	0	—	6.95	32	84	62	3.4	1.7
20	Myotonia dystrophica	41	—	0	—	5.75	38	88	62	3.4	1.7
21	Spinal muscular atrophy	66	—	0	—	6.38	20	132	88	3.9	2.0
22	Multiple sclerosis	20	—	15	+	7.08	23	130	68	3.8	2.2
	Multiple sclerosis	29	—	4	2+	6.85	60	84	44	3.6	1.2

* S. C. D. indicates secondary cord degeneration.

TABLE 3 (Group N).—*Patients with Miscellaneous Non-Neurologic Surgical Conditions*

Patien No.	Diagnosis	Age, Yr.	Protein		Sugar, Mg./100 Cc.		Phosphorus, Mg./100 Cc.	
			Serum, Gm./100 Cc.	CSF, Mg./100 Cc.	Serum	CSF	Serum	CSF
1	Uterine fibroid	46	6.5	25	172	62	3.9	1.9
2	Rectal fistula	47	7.4	25	68	36	3.0	2.0
3	Anal fistula	66	7.2	24	56	56	3.1	2.1
4	Hemorrhoids	15	7.6	14	80	54	6.2	2.0
5	Diabetes with gangrene of toe	77	7.3	47	120	20	3.1	2.0
6	Benign prostatic hypertrophy	72	7.6	39	92	54	6.5	1.9
7	Hemorrhoids	39	7.1	47	68	28	3.4	1.9
8	Hemorrhoids	49	8.4	..	20	44	4.2	2.2
9	Hemorrhoids	37	7.8	26	62	48	2.4	2.1
10	Inguinal hernia	25	7.4	26	20	48	3.3	2.5
11	Acute appendicitis	22	7.8	47	46	54	4.1	2.5
12	Benign prostatic hypertrophy	66	7.3	30	100	58	6.1	2.3
13	Tubovarian abscess	52	7.1	15	152	96	4.4	2.4
14	Gangrene of toe	62	6.3	9	124	54	3.3	2.2
15	Carcinoma of cervix	27	7.3	21	72	62	4.2	2.1
16	Uterine fibroid	38	7.0	16	54	48	4.0	2.0

spinal fluid findings, in the comments on the various diagnostic groups.

In Table 4 are presented our findings of the individual inorganic phosphorus values in the cerebrospinal fluid, together with the corresponding blood serum phosphorus values, arranged according to their diagnosis. The statistical analysis of the cerebrospinal fluid phosphorus values is shown in Table 5. In Table 6 is shown the statistical significance of the differences in the results obtained. Table 7 shows in each diagnostic group the proportion of cases with elevated cerebrospinal fluid phosphorus values, as well as the statistical significance of those varying proportions.

On examining Tables 4 and 5, it becomes evident that Groups A, B, C, D, and E have many characteristics in common. The indi-

TABLE 4.—*Individual Inorganic Phosphorus Values of Cerebrospinal Fluids and Corresponding Blood Serums Arranged According to Diagnostic Groups*

Group	Diagnosis	Phosphorus Values, (Mg./100 Cc.) in Cerebrospinal Fluid Specimens and (in brackets) in Corresponding Blood Serum Specimens
A	Meningism	1.4 (4.8), 1.5 (5.1), 1.7 (5.1), 2.0 (5.3), 1.7 (...), 2.2 (6.7), 1.4 (4.4), 1.5 (4.1), 1.3 (4.0), 1.4 (4.1), 1.7 (4.1), 1.2 (4.8), 1.3 (4.8), 1.6 (3.7)
B	Febrile convulsions	1.9 (7.6), 1.7 (5.7), 1.6 (4.1), 1.8 (4.2), 1.6 (3.9), 1.6 (5.3), 1.2 (3.3), 1.7 (5.0)
C	Pulmonary and miliary t. b.	1.5 (5.2), 1.6 (3.1), 1.5 (5.9), 1.5 (4.3), 1.7 (4.4), 1.6 (3.4), 1.6 (4.6), 1.6 (5.2), 2.0 (4.4), 2.0 (5.0), 1.4 (4.1)
D	Mental retardation	1.6 (4.1), 1.4 (4.1), 1.7 (5.8), 1.6 (...), 1.6 (3.9), 1.7 (6.9), 1.5 (...), 1.6 (4.4), 1.7 (5.2), 2.2 (6.5), 1.7 (4.9), 1.9 (5.7), 1.6 (5.3), 1.7 (4.8), 1.6 (5.9), 1.7 (5.4), 1.5 (5.9), 1.6 (5.2), 1.8 (5.9), 1.3 (5.7), 1.5 (4.3), 1.7 (4.9), 1.3 (5.0), 1.3 (4.5)
E	Epilepsy	1.6 (4.1), 1.6 (...), 1.5 (3.6), 1.7 (...), 1.8 (3.3), 1.2 (...), 1.6 (3.0), 1.7 (3.8), 1.9 (4.1), 0.9 (2.7), 2.0 (2.2), 2.0 (3.0), 1.5 (5.2)
F	Tuberculous meningitis	2.7 (3.3), 2.7 (...), 2.2 (...), 1.4 (4.1), 4.4 (5.1), 3.0 (5.1), 1.7 (4.8), 2.4 (4.2), 2.0 (5.7), 2.3 (4.8), 2.3 (4.3), 3.6 (8.9), 3.1 (4.8), 2.2 (3.9), 2.4 (6.2), 2.9 (5.7), 4.1 (5.5), 2.0 (4.4), 2.5 (3.4), 2.8 (4.4), 3.3 (4.7), 2.3 (3.9), 2.7 (4.1), 2.2 (...), 2.7 (5.3), 3.1 (5.3), 2.3 (4.2), 2.7 (6.4), 4.1 (5.4), 4.2 (4.8), 3.8 (5.3), 3.4 (5.5), 3.0 (5.3), 3.0 (...), 2.7 (4.4), 3.0 (5.7), 2.2 (4.3), 2.5 (6.0), 2.2 (5.7), 1.8 (...), 2.8 (4.2), 3.4 (4.3), 2.7 (3.0), 2.5 (5.9), 2.8 (4.7), 3.9 (5.6), 2.7 (4.6), 3.3 (4.4), 2.7 (...)
G	Purulent meningitis	2.4 (6.4), 1.7 (4.0), 2.1 (4.5), 3.7 (5.3), 3.9 (3.9), 2.8 (3.2), 2.0 (4.1), 2.1 (...), 1.9 (3.9), 1.8 (4.6), 1.1 (...), 1.9 (4.2), 1.0 (...), 2.1 (3.2)
H	Poliomyelitis	1.5 (4.2), 2.0 (3.2), 2.0 (4.7), 2.2 (5.3), 2.2 (5.2), 2.0 (4.0), 2.1 (4.4), 2.2 (4.2), 2.5 (6.1), 2.4 (5.2), 2.4 (4.2), 2.4 (5.5), 2.0 (4.9)
I	Acute encephalitis	2.4 (5.5), 2.4 (3.3), 2.1 (6.7), 2.3 (4.8), 1.9 (5.0), 3.1 (3.4)
J	C. N. S. syphilis	1.5 (4.1), 2.1 (5.2), 1.4 (5.4), 1.6 (3.3), 2.0 (...)
K	C. N. S. manifestations of alcoholism	1.3 (2.4), 1.8 (3.1), 1.5 (3.3), 1.7 (2.8), 1.5 (3.1), 1.8 (...), 1.8 (2.8), 1.1 (2.1), 1.1 (2.9), 1.5 (2.5), 2.1 (3.2), 1.4 (4.8), 1.4 (2.8), 1.4 (3.1)
L	C. N. S. arteriosclerosis	2.1 (4.8), 2.0 (...), 1.9 (3.3), 1.9 (3.5), 1.9 (3.0), 2.5 (...)
M	Miscellaneous neurologic conditions	1.7 (4.8), 1.6 (3.0), 1.6 (3.3), 1.7 (3.0), 1.3 (5.6), 2.2 (3.8), 1.7 (3.1), 1.9 (...), 1.6 (5.1), 1.8 (4.3), 1.8 (2.8), 3.8 (4.1), 2.5 (4.8), 1.5 (...), 2.7 (4.3), 1.7 (4.6), 1.7 (...), 2.2 (2.4), 1.7 (3.4), 1.7 (3.4), 2.0 (3.9), 2.2 (3.8), 1.2 (3.6)
N	Miscellaneous non-neurologic conditions	1.9 (3.9), 2.0 (3.0), 2.1 (3.1), 2.0 (6.2), 2.0 (3.1), 1.9 (6.5), 1.9 (3.4), 2.2 (4.2), 2.1 (2.4), 2.5 (3.3), 2.5 (4.1), 2.3 (6.1), 2.4 (4.4), 2.2 (3.3), 2.1 (4.2), 2.0 (4.0)

vidual phosphorus values are practically all between 1.2 and 2.0 mg. per 100 cc., with the exception of two values that reached 2.2 mg. per 100 cc. (Table 4). The means of these five groups vary narrowly between 1.564 and 1.638 mg. per 100 cc. (Table 5). From the clinical point of view, all members of these groups showed no evidence of any actively destructive or progressive neurologic disorder. The laboratory examinations also showed, in every case, completely normal cerebrospinal fluid, as judged by the accepted criteria of normality. These five groups may, therefore, be considered together as being made up of neurologically normal subjects. This large composite group (A-E) will, thus, serve as our "normal" group for the purpose of establishing our normal values. It will also serve as a basis of comparison for the results of the other groups, with regard to their normality or otherwise.

Normal Group.—Figure 1 shows the frequency distribution of the values of cerebrospinal fluid phosphorus in this composite "normal" group (A-E). It is seen that the peak incidence is at the 1.6 mg. per 100 cc. value, and the scatter of the phosphorus values around 1.6 mg. per 100 cc. is more or less symmetrical. Only one value falls below 1.2 mg. per 100 cc., and only two values fall above 2.0 mg. per 100 cc. One thus seems justified in considering 1.6 mg. per 100 cc. as the normal average cerebrospinal fluid phosphorus value and 1.2-2.0 mg. per 100 cc. as the normal range. Similar conclusions may be drawn from the statistical analysis of this composite group. As is seen in Table 5, the mean for Group A-E is found to be 1.611 mg. per 100 cc.; the standard deviation, 0.2321, and the standard error of the mean, 0.02794. The mean of each of the individual diagnostic groups A, B, C, D, and E, which constitute the composite "normal" group (A-E), does not differ significantly from the mean of this composite group itself (Table 6).

Tuberculous Meningitis.—By comparison, the frequency distribution of the cerebrospinal fluid phosphorus values in tuberculous meningitis (Group F) is illustrated in Figure 2.

TABLE 5.—*Statistical Analysis of Cerebrospinal Fluid Phosphorus Values of the Various Diagnostic Groups*

Group	Diagnosis	No. of Specimens	Range, Mg./100 Cc.	Mean, Mg./100 Cc.	Standard Deviation	Standard Error of Mean
A	Meningism	14	1.2-2.2	1.564	0.2686	0.07449
B	Febrile convulsions	8	1.2-1.9	1.638	0.1936	0.07317
C	Pulmonary and miliary t. b.	11	1.4-2.0	1.636	0.1871	0.05917
D	Mental retardation	24	1.3-2.2	1.617	0.1926	0.04016
E	Epilepsy	13	0.9-2.0	1.615	0.2961	0.08548
F	Tuberculous meningitis	49	1.4-4.4	2.790	0.6584	0.09503
G	Purulent meningitis	14	1.0-3.9	2.179	0.7948	0.2204
H	Poliomyelitis	13	1.5-2.5	2.146	0.2527	0.07295
I	Acute encephalitis	6	0.9-3.1	2.367	0.3719	0.1663
J	C. N. S. syphilis	5	1.4-2.1	1.720	0.2786	0.1246
K	C. N. S. manifestations chronic alcoholism	14	1.1-2.1	1.529	0.2739	0.07596
L	C. N. S. arteriosclerosis	6	1.9-2.5	2.050	0.2140	0.08736
M	Miscellaneous neurologic disease	23	1.2-3.8	1.905	0.5282	0.1101
N	Miscellaneous non-neurologic conditions	16	1.9-2.5	2.131	0.1959	0.05058
A-E ("Normal")		70	0.9-2.2	1.611	0.2321	0.02794

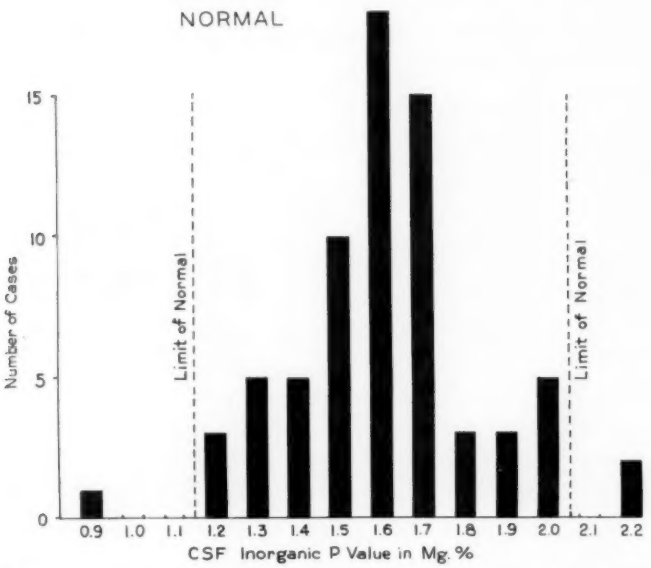

Fig. 1.—Frequency distribution of the cerebrospinal fluid inorganic phosphorus values of the composite "normal" group.

As seen in this diagram, all phosphorus values, with the exception of five, fall above 2.0 mg. per 100 cc. The peak incidence is at the 2.7-2.8 mg. per 100 cc. level, and the scatter around this peak is roughly symmetrical. The statistical analysis of this group shows the range to be 1.4 to 4.4 mg. per 100 cc., with a mean of 2.790 mg. per 100 cc., a standard deviation of 0.6584, and a standard error of the mean of 0.09503 (Table 5). The mean of this group differs from the "normal" mean by 1.179, which is very highly significant statistically (Table 6). About 90% of values in this group were found to be elevated beyond the limits of normality, a value which is also very highly significant statistically (Table 7).

Purulent Meningitis.—Figure 3 illustrates the frequency distribution of the cerebrospinal fluid phosphorus values in purulent meningitis (Group G). The peak incidence is seen to be in the normal range of 1.6 to

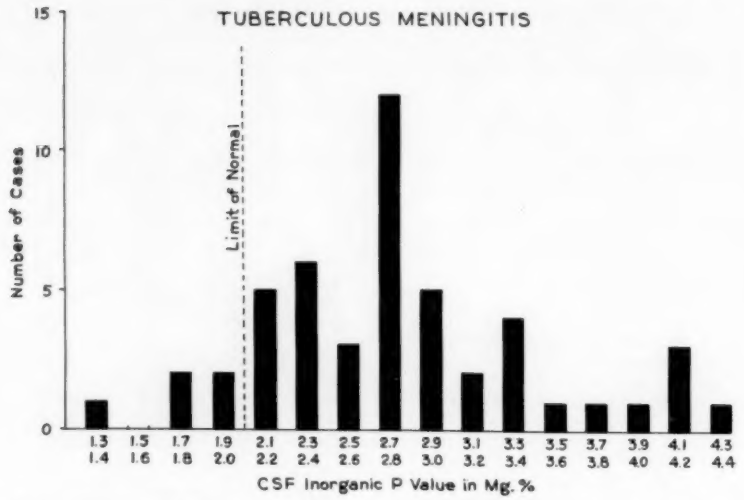

Fig. 2.—Frequency distribution of the cerebrospinal fluid inorganic phosphorus values of the tuberculous meningitis group.

TABLE 6.—*Statistical Significance of Differences in the Mean Cerebrospinal Fluid Phosphorus Values of the Various Groups As Compared with Values for the Normal Group (A-E)*

Group	Diagnosis	Mean C. S. F. P Value, Mg./100 Cc.	Difference Between Mean of Group and Mean of Normal Group (A-E)	Standard Error of Difference Between the Two Means	No. of Times Difference Is Greater Than Its Standard Error	Statistical Significance of Difference Between the Two Means
A-E	"Normal"	1.611	.....	.....	...	.....
A	Meningism	1.564	0.047	0.07956	0.6	Not significant
B	Febrile convulsion	1.638	0.027	0.07832	0.3	Not significant
C	Pulmonary and miliary t. b.	1,636	0.025	0.06543	0.4	Not significant
D	Mental retardation	1.617	0.008	0.04892	0.2	Not significant
E	Epilepsy	1,615	0.004	0.08993	0.04	Not significant
F	Tuberculous meningitis	2.790	1.179	0.09805	12.0	Very highly significant
G	Purulent meningitis	2.179	0.568	0.2222	2.6	Significant
H	Poliomyelitis	2.146	0.535	0.07812	6.8	Very highly significant
I	Acute encephalitis	2.367	0.756	0.1686	4.5	Highly significant
J	C. N. S. syphilis	1.720	0.109	0.1277	0.8	Not significant
K	C. N. S. manifestations of chronic alcoholism	1.529	0.082	0.08093	1.0	Not significant
L	C. N. S. arteriosclerosis	2.050	0.439	0.09172	4.8	Highly significant
M	Misc. neurological conditions	1.905	0.294	0.1136	2.6	Significant
N	Misc. non-neurological conditions	2.131	0.520	0.05778	9.2	Very highly significant

2.0 mg. per 100 cc., but a large proportion of values is seen to fall above 2.0 mg. per 100 cc. The statistical analysis of the data of this group shows the range to be 1.0 to 3.9 mg. per 100 cc., with a mean of 2.179 mg. per 100 cc., a standard deviation of 0.7948, and a standard error of the mean of 0.2204 (Table 5). The mean of this group differs from the mean of the "normal" group by 0.568, which is definitely significant statistically (Table 6). The proportion of elevated phosphorus values in this group is 50%, which is highly significant statistically (Table 7).

Poliomyelitis.—Figure 4 illustrates the frequency distribution of the cerebrospinal fluid phosphorus values in poliomyelitis (Group H). As is seen in this diagram, the peak incidence is in the 2.0 mg. per 100 cc. value, but the majority of values fall above this dividing line. Statistical analysis of the data of this group shows the range to be 1.5 to 2.5 mg. per 100 cc., with a mean of 2.146 mg.

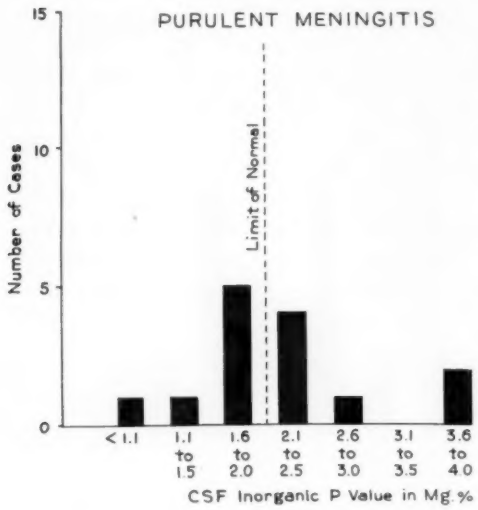

Fig. 3.—Frequency distribution of the cerebrospinal fluid inorganic phosphorus values of the purulent meningitis group.

per 100 cc., a standard deviation of 0.2527, and a standard error of the mean of 0.07295 (Table 5). The mean of this group differs from the mean of the "normal" group by 0.535, which is highly significant (Table 6). The proportion of abnormally elevated values in this group is 62%, which is also highly significant statistically (Table 7).

Acute Encephalitis (Group I).—The range of phosphorus values is 0.9 to 3.1 mg. per 100 cc., with a mean of 2.367, a standard deviation of 0.3719, and a standard error of the mean of 0.1663 (Table 5). The mean of this group differs from the mean of the "normal" group by 0.756, which is highly significant (Table 6). The proportion of abnormally elevated values in this group is 83%, which is also highly significant (Table 7).

Central Nervous System Syphilis (Group J).—The range of phosphorus values is 1.4 to 2.1 mg. per 100 cc., with a mean of 1.720 mg. per 100 cc., a standard deviation of 0.2786, and a standard error of the mean of 0.1246 (Table 5). The mean of this group differs from the mean of the "normal" group by 0.109, which is not statistically significant (Table 6). The proportion of elevated phosphorus values in this group is 7%, which is also not significant statistically (Table 7).

Central Nervous System Manifestations of Chronic Alcoholism (Group K).—The range of phosphorus values is 1.1 to 2.1 mg. per 100 cc., with a mean of 1.529 mg. per 100 cc., a standard deviation of 0.2739, and a standard error of the mean of 0.07596 (Table 5). The mean of this group differs from the mean

TABLE 7.—*Proportion of Cerebrospinal Fluid Specimens with Elevated Phosphorus Content in the Various Diagnostic Groups and Its Statistical Significance*

Group	Diagnosis	No. of Specimens	No. with Normal P Content (i. e., Less Than 2.0 Mg./100 Cc.)	No. with Elevated P Content (i. e., More Than 2.0 Mg./100 Cc.)	Percentage with Increased P Content	χ^2	P	Statistical Significance
A-E	"Normal"	70	68	2	3	. .	.....	.....
A	Meningism	14	13	1	7	0.6	>0.30	Not significant
B	Febrile convulsion	8	8	0	0	0.2	>0.50	Not significant
C	Pulmonary and miliary t. b.	11	11	0	0	0.3	>0.50	Not significant
D	Mental retardation	24	23	1	4	0.02	>0.80	Not significant
E	Epilepsy	13	13	0	0	0.3	>0.50	Not significant
F	Tuberculous meningitis	49	5	44	90	85.8	>0.01	Highly significant
G	Purulent meningitis	14	7	7	50	27.1	>0.01	Highly significant
H	Poliomyelitis	13	5	8	62	35.6	>0.01	Highly significant
I	Acute encephalitis	6	1	5	83	42.8	>0.01	Highly significant
J	C. N. S. syphilis	5	4	1	20	3.6	>0.05	Not significant
K	C. N. S. manifestations of chronic alcoholism	14	13	1	7	0.6	>0.30	Not significant
L	C. N. S. arteriosclerosis	6	4	2	33	10.3	>0.01	Highly sifnificant
M	Misc. neurologic diseases	23	17	6	26	8.8	>0.01	Highly significant
N	Misc. non-neurologic conditions	16	7	9	56	33.3	>0.01	Highly significant

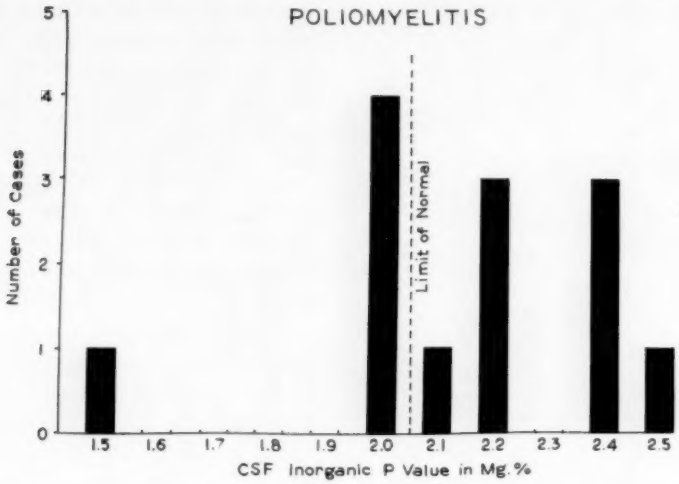

Fig. 4.—Frequency distribution of the cerebrospinal fluid inorganic phosphorus values of the poliomyelitis group.

of the "normal" group by 0.082, which is not statistically significant (Table 6). The proportion of elevated phosphorus values in this group is 7%, which is also not significant statistically (Table 7).

Central Nervous System Arteriosclerosis (Group L).—The range of phosphorus values is 1.9 to 2.5 mg. per 100 cc., with a mean of 2.050 mg. per 100 cc., a standard deviation of 0.2140, and a standard error of the mean of 0.08736 (Table 5). The mean of this group differs from the mean of the "normal" group by 0.439, which is highly significant statistically (Table 6). The proportion of elevated phosphorus values in this group is 33%, which is also significant statistically (Table 7).

Miscellaneous Neurologic Conditions (Group M).—This group shows a mean of 1.905 mg. per 100 cc. (Table 5). The cases of this group, however, have to be viewed individually, since the diagnoses differ from case to case. As is seen in Table 2, elevated cerebrospinal fluid phosphorus values were found in one case of each of the following conditions: cerebral birth injury in the acute stage, cord tumor, compression myelitis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, and multiple sclerosis.

Miscellaneous Non-Neurologic Conditions (Group N).—In this group, consisting of presurgical specimens of cerebrospinal fluid removed prior to spinal anesthesia, the range of phosphorus values is 1.9 to 2.5 mg. per 100 cc., with a mean of 2.131 mg. per 100 cc., a standard deviation of 0.1959, and a standard error of the mean of 0.05058 (Table 5). The mean of this group differs from the mean of the "normal" group by 0.520, which is very highly significant statistically (Table 6). The proportion of elevated phosphorus values in this group is 56%, which is also very highly significant statistically (Table 7). Figure 5 illustrates the frequency distribution

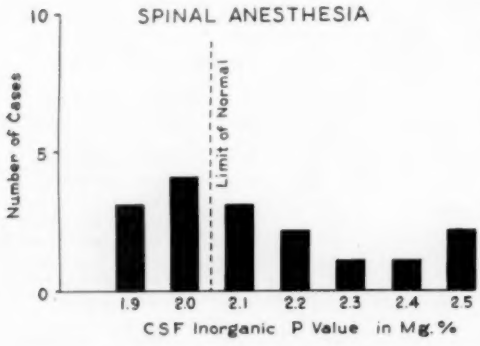

Fig. 5.—Frequency distribution of the cerebrospinal fluid inorganic phosphorus values of the spinal anesthesia group (Group N).

of the cerebrospinal phosphorus values in this group.

Summary.—The statistical analysis of our data revealed that cerebrospinal fluid phosphorus was significantly elevated in tuberculous meningitis, purulent meningitis, poliomyelitis, acute encephalitis, central nervous system arteriosclerosis, and, mysteriously enough, in the presurgery group (N). In the other diagnostic groups the cerebrospinal fluid phosphorus was not significantly altered.

COMMENT

Normal Cerebrospinal Fluid Phosphorus Content

It has been pointed out [16] that the process of establishing normal values for cerebrospinal fluid components is hampered by the fact that no spinal taps are ever performed on completely normal persons. As a matter of fact, cerebrospinal fluid is removed for examination only when some central nervous system involvement is definitely suspected. It is apparent that the criteria of normality of a cerebrospinal fluid specimen are to be looked for primarily in the results of the analysis of the cerebrospinal fluid itself, and only secondarily in the diagnosis of the patient. For general purposes, a cerebrospinal fluid specimen is considered as normal when it contains no cells, gives a negative Kahn test and Pandy test, and has normal glucose and protein values.

In establishing our "normal" group, we utilized these same criteria. As we stated previously, all cerebrospinal fluid specimens included in Groups A, B, C, D, and E were normal as judged by the above accepted criteria of normality. In addition, however, certain clinical criteria were also employed. In Groups A to E were included only those patients who showed no clinical evidence of any actively progressive or destructive disease of the central nervous system, whether inflammatory, degenerative, or vascular in origin. However, patients with a fixed, long-standing, nonprogressive, residual lesion of the central nervous system, such as in cases of mental retardation following cerebral birth injury, were not excluded from these groups.

On the basis of the results obtained in this large composite group (A-E), the average normal cerebrospinal fluid phosphorus was found to be 1.6 mg. per 100 cc., with a range of normals between 1.2 and 2.0 mg. per 100 cc. These normal values agree with those of most other authors, although, on the whole, the number of normal cerebrospinal fluid phosphorus values in the literature is rather small. Odessky [19] compiled from the literature all the normal values of cerebrospinal fluid phosphorus and found a total of only 170 determinations. In 165 of these, phosphorus values were 2.0 mg. per 100 cc. or less, while in only 5 were they over 2.0 mg. per 100 cc. The mean inorganic phosphorus values found by the different authors ranged from 1.2 to 1.7 mg. per 100 cc. Odessky and associates [19] found a mean cerebrospinal fluid phosphorus of 1.4 mg. per 100 cc. among 22 normal subjects, for whom the values ranged from 0.9 to 2.0 mg. per 100 cc. Our findings for normal cerebrospinal fluid phosphorus values thus agree with those in the literature.

Abnormal Cerebrospinal Fluid Phosphorus Content

Elevated cerebrospinal phosphorus values have been reported in inflammatory conditions of the central nervous system, whether bacterial, viral, or spirochetal. However, neurologic conditions other than of inflammatory origin have also occasionally been reported to be associated with elevated cerebrospinal fluid phosphorus. Table 8 shows the various neurologic conditions in which elevated cerebrospinal fluid phosphorus was reported in the literature, together with the names of the authors who reported them.

Our findings of elevated cerebrospinal fluid phosphorus values in various pathologic conditions of the central nervous system in part corroborate those of others, in part contrast with those of others, and in part are reported for the first time. Elevated cerebrospinal fluid phosphorus values were found by us most consistently in inflammatory conditions, notably in tuberculous meningitis and purulent meningitis, thus confirming the findings of others. In contrast

TABLE 8.—*Neurologic Conditions in Which Elevated Cerebrospinal Fluid Phosphorus Was Reported in the Literature*

Author	Neurologic Conditions in Which Elevated C. S. F. Inorganic Phosphorus Was Found																		
	Tuberculous Meningitis	Purulent Meningitis	Measles Encephalitis	Mumps Encephalitis	Varicella Encephalitis	Pertussis Encephalopathy	Toxic Encephalitis	Poliomyelitis	Syphilitic Meningitis	Dementia Paralytica	Tabes Dorsalis	Neurosyphilis	Polyneuritis	Compression Myelitis	Hydrocephalus	Uremia	Cerebral Tumor	Delirium Tremens	Familial Amaurotic Idiocy
Donath [17]	..	..	..	..	..	.	..	..	..	x	x	..	..	..	..	..	x	..	..
Apelt and Schuman [18]	x	..	..	..	..	..	..	..	..	x	..	..	..	..	..	x	x	x	..
Barrio [19]	..	..	..	..	..	..	..	..	..	..	x	x	..	..	..	..	..	..	..
Cohen [5]	x	x	..	..	..	..	..	..	x	x	..	..	..	x	..	..	x	..	..
Behrendt and Helm [20]	x	x	..	..	..	x	x	..	..	..	..	..	..	..	x	..	..	..	x
Steiner [21]	x	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Merritt and Bauer [22]	x	..	..	..	..	..	..	..	..	..	..	..	x	..	..	..	..	..	..
Cohn and others [6]	x	x	..	..	..	..	..	..	..	..	..	..	..	..	x	..	x	..	..
Garsche and Souchon [8]	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Ragazzini [9]	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Odessky and others [10]	..	..	x	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Odessky and others [11]	..	..	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Odessky and others [12]	..	..	..	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Odessky and others [13]	..	..	..	..	..	..	..	x	..	..	..	..	..	..	..	..	..	..	..
Odessky and Rosenblatt [14]	..	x	..	..	x	..	..	..	..	..	..	..	..	..	..	..	..	..	..

to others,† we found no elevation of cerebrospinal fluid phosphorus in syphilis of the central nervous system, but the number of cases was too small to enable us to draw valid conclusions. We, however, found a consistent elevation of the cerebrospinal fluid phosphorus in cerebral arteriosclerosis, a value which was statistically highly significant. This finding has not been reported previously. We also found elevated cerebrospinal fluid phosphorus in isolated cases of recent cerebral birth injury, cord tumor, compression myelitis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, and multiple sclerosis. With one exception, namely, compression myelitis, there are no reports in the literature of similar findings.

RELATION OF CEREBROSPINAL FLUID PHOSPHORUS TO BLOOD SERUM PHOSPHORUS

The question of the relationship between the cerebrospinal fluid phosphorus and blood serum phosphorus has drawn the attention of many investigators. This is evidenced by the relatively large amount of literature that has accumulated on the subject. The findings of these various authors have been amply reviewed by Katzenelbogen.[4] He summarized these views by saying that no constant relationship was found between the inorganic phosphorus content of the cerebrospinal fluid and that of the blood serum. Our findings in regard to the relationship of the inorganic phosphorus value of the cerebrospinal fluid to that of the blood is illustrated in Figure 6. As is obvious at a glance, no linear relationship can be seen to exist between the two corresponding values. The same blood serum phosphorus value may be seen to be

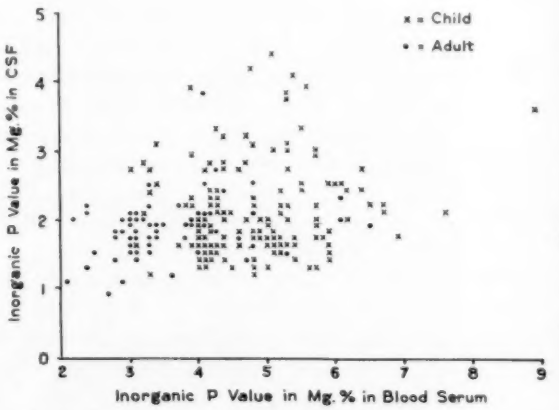

Fig. 6.—Relationship of the individual inorganic phosphorus values in the cerebrospinal fluid to their corresponding phosphorus values in the blood serum.

† References 5 and 17 to 19.

associated with a normal cerebrospinal fluid phosphorus as with a markedly elevated value and vice versa. No correlation of significance can, therefore, be established between the blood serum phosphorus and the cerebrospinal fluid phosphorus. Each apparently behaves in a completely independent manner. Our findings are thus in agreement with those in the literature.

Relation of Cerebrospinal Fluid Phosphorus to Cerebrospinal Fluid Protein

The relationship between the cerebrospinal fluid inorganic phosphorus and the cerebrospinal fluid protein values is also of considerable interest. In Figure 7 are illustrated graphically our findings concerning this relationship in Groups F, G, H, I, and L., the groups in which the cerebrospinal fluid inorganic phosphorus values were, on the whole, elevated. It is seen in Figure 7 that, although some elevated cerebrospinal phosphorus values are associated with normal cerebrospinal fluid protein values (*area "A"* in diagram), and some elevated protein values are associated with normal phosphorus values (*area "B"* in diagram), yet the great majority of elevated cerebrospinal fluid phosphorus values are associated with elevated protein values (*area "C"* in diagram). Figure 7, thus, demonstrates that a definite correlation exists between these two components of the cerebrospinal fluid. This does not mean, however, that this relationship is one of cause and effect. In other words, the elevated cerebrospinal phosphorus content is not necessarily the result of an elevated cerebrospinal fluid protein content, or vice versa. On the contrary, it is much more likely, in our opinion, that both components become elevated as a result of the same causative factor.

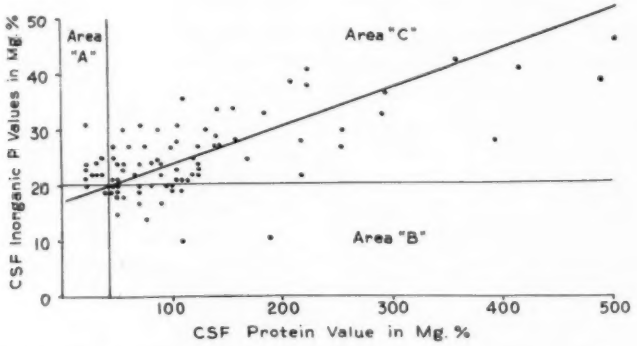

Fig. 7.—Relationship of the cerebrospinal fluid inorganic phosphorus value to the corresponding cerebrospinal fluid protein value in Groups F, G, H. I, and L.

General Considerations

The problem of the mechanism by means of which the cerebrospinal fluid phosphorus becomes elevated in certain pathologic conditions of the central nervous system has greatly intrigued investigators in this field. Generally speaking, the increase in cerebrospinal fluid phosphorus may originate from one of two sources. It may originate in the blood stream through a disturbance in the blood-cerebrospinal fluid barrier. It may, however, also originate in the nervous system itself, as a result of the breakdown of nerve tissue, which is rich in phosphorus.

In the consideration of a disturbance in the blood-brain barrier, a number of possibilities are to be taken into account. The phosphorus may become raised through excessive secretion or filtration of phosphorus by the choroid plexuses in the cerebrospinal fluid, while the absorptive capacity of the arachnoid villi remains unaltered. The cerebrospinal fluid phosphorus may also become elevated by the opposite mechanism—namely, the absorptive capacity of the arachnoid villi becomes deficient while the secretory capacity of the choroid plexuses remains

unaltered. Finally, the phosphorus may become elevated through a combined mechanism, namely, increased secretion and decreased absorption. One of the arguments against a disturbance in the blood-brain barrier as the mechanism of elevating the cerebrospinal phosphorus is that it is not conceivable that such a change should affect phosphorus only. If any one of these possibilities were the true mechanism, one would expect the raised phosphorus value to go hand in hand with raised values of the other inorganic components of the cerebrospinal fluid, notably sodium, potassium, chloride, etc. This, however, does not occur.‡

The theory of a disturbance in the blood-brain barrier as a cause of elevated cerebrospinal fluid phosphorus has, nevertheless, been accepted by many authors. It certainly would explain in a fairly plausible manner the rise in cerebrospinal fluid phosphorus in meningitis, in which altered conditions in the blood-brain barrier are known to exist. However, in other conditions in which elevated cerebrospinal fluid phosphorus has been found, no altered permeability of the choroid plexuses or of the arachnoid villi has ever been demonstrated. In these nonmeningitic cases, therefore, another mechanism must be invoked in order to explain the rise in the cerebrospinal fluid phosphorus.

It seems inconceivable that the mechanism of elevation of the cerebrospinal fluid inorganic phosphrous should be different in different pathologic conditions. It is hard to explain the phosphorus elevation in meningitis as being on the basis of increased permeability of the choroid plexuses while in other conditions it is due to some other mechanism. Rather than that, it seems to us more logical to look for a factor common to all the pathologic conditions which are accompanied by elevated cerebrospinal fluid phosphorus values. This common factor is obviously not the altered permeability of the choroid plexuses or of the arachnoid villi. It appears to us that the only factor common to all the conditions accompanied by elevated phosphorus values is destruction of nerve tissue.

The presence of elevated cerebrospinal fluid inorganic phosphorus, not only in inflammatory conditions of the brain and its coverings but also in processes of a completely different nature, such as brain tumor, birth injury, hydrocephalus, cerebral vascular accidents, multiple sclerosis, cerebral arteriosclerosis, amyotrophic lateral sclerosis, and cord tumor, is thus, in our opinion, irrefutable evidence that the origin of the raised phosphorus values is to be sought not in the blood-brain barrier but in the central nervous system itself. In all these conditions, a breakdown of nerve tissue takes place, and it is this destruction of nerve tissue, by whatever process that may be—inflammatory, traumatic, vascular, degenerative, or neoplastic—that causes the rise in the cerebrospinal fluid inorganic phosphorus.

One thing that remains to be explained, on the basis of the tissue breakdown theory, is why cerebrospinal fluid phosphorus is consistently elevated only in inflammatory processes, while in other conditions the phosphorus values are very variable. The answer to this is to be found in the rate and degree of activity of the destructive process. In acute conditions the amount of tissue destroyed per unit of time is most probably much higher than in the chronic, protracted conditions. The degree of elevation will, therefore, be higher in the acute cases. Moreover, there is considerable temporal variability in the activity of chronic processes with remissions and exacerbations. This would result in variable degrees of destruction and various levels of cerebrospinal fluid inorganic phosphorus at various times. This would explain why in some cases of multiple sclerosis, for example, the phosphorus is elevated while in others it is normal.

No logical explanation can be found for the statistically significant elevation of the phosphorus values in the patients in whom the cerebrospinal fluid was obtained in preparation for spinal anesthesia. So far, similar elevations of phosphorus in spinal anesthesia specimens have not been reported in the

‡ Unpublished data.

literature. If our findings are corroborated, they would point to the inadvisability of considering spinal anesthesia specimens as the prototype of normal cerebrospinal fluid.

That increased cerebrospinal fluid phosphorus in various pathologic conditions of the central nervous system is due to the breakdown of brain tissue finds support in recent studies on autolysis in the cerebrospinal fluid.

Indirect evidence of autolysis may be gleaned from the fact that various enzymes were reported to be present in the cerebrospinal fluid. The literature on this subject has been reviewed by Kafka,[3] who summarized it by saying that in normal cerebrospinal fluid small amounts of amylase, lipase, and oxidase are present. In pathologic cerebrospinal fluid these ferments are increased in amount, and other enzymes, namely, tryptase, peptase, catalase, and peroxidase, can also be found. The presence of these various enzymes in the cerebrospinal fluid would seem to indicate that active metabolic processes occur in the cerebrospinal fluid in certain pathologic conditions of the central nervous system. The chemical changes observed in the cerebrospinal fluid in pathologic conditions are, therefore, not to be dismissed as mere products of physical filtration from the blood. It would, rather, appear that the changes observed are most probably the result of definite metabolic reactions occurring in the cerebrospinal fluid and in the brain substance.

In this respect, phosphatase activity in the cerebrospinal fluid is of particular interest, since phosphatase is related to the metabolism of phosphorus and phosphorus-containing material. This aspect of the cerebrospinal fluid was studied by Fleischhacker,[23] Kaplan and associates,§ and Colling and Rossiter,[26] all of them reporting the presence of low concentration of alkaline phosphatase in normal cerebrospinal fluid. Colling and Rossiter [26] also reported the presence of an acid phosphatase in many normal cerebrospinal fluids. An increase in alkaline phosphatase activity of cerebrospinal fluid from patients with purulent meningitis, tuberculous meningitis, and poliomyelitis was reported by Kaplan and associates.[24] This was confirmed by Colling and Rossiter,[26] who found an increase also in the acid phosphatase of cerebrospinal fluid from patients with meningitis and poliomyelitis. This increase in phosphatase activity would be expected to be associated with increased phosphorus metabolism, possibly in the nature of the breakdown of phosphorus-containing organic compounds of the brain tissue.

Cohen [5] studied evidence of autolysis in the cerebrospinal fluid after death. Estimations of cerebrospinal fluid phosphorus were carried out on 10 postmortem specimens, and values far exceeding those normally present in the blood were found. The results obtained varied from 5.41 mg. per 100 cc., in a specimen obtained 3 hours after death, to 14.8 mg. per 100 cc., in a specimen obtained 20 hours after death. Cohen concluded that the marked increase in the organic phosphorus content of cerebrospinal fluid after death could be explained only on the basis of autolysis of nerve tissue. Cohen found further evidence for postmortem autolysis of nerve tissue in nonprotein-nitrogen content of cerebrospinal fluid, which normally is 20-30 mg. per 100 cc. Some hours after death Cohen found amounts between 200 and 400 mg. per 100 cc.

Kafka [3] was the first to study direct evidence of autolysis in the cerebrospinal fluid during life. He used two different approaches. He investigated the presence in the cerebrospinal fluid of the autolytic ferment endoprotease and demonstrated that in the cerebrospinal fluid a very slight degree of autolysis may occur. Later, however, he concluded that the slight increase in nitrogen was probably not due to autolysis. Kafka also investigated the presence in the cerebrospinal fluid of antienzymes which inhibit autolysis but could not discover any.

Kovacs [27] investigated evidence of autolysis in the cerebrospinal fluid by using an entirely new approach. He studied the variations in inorganic phosphorus concentration of cerebrospinal fluid before and after in-

§ References 24 and 25.

cubation under sterile conditions. Normal cerebrospinal fluid exhibited no change in the inorganic phosphorus after incubation as compared with the preincubation level, nor did specimens from neurologically normal persons. By contrast, in acute bacterial meningitis a great increase in phosphorus was usually evident after incubation. Increases in cerebrospinal fluid phosphorus after incubation, as compared with preincubation levels, were also found in neurosyphilis, tabes, dementia paralytica, mumps encephalitis, Guillain-Barré syndrome, brain tumor, post-traumatic syndrome, and idiopathic epilepsy. No increase in cerebrospinal fluid phosphorus following incubation was found in "symptomatic" convulsions, lymphocytic choriomeningitis, and poliomyelitis.

The rise, in certain pathologic conditions, of the cerebrospinal fluid inorganic phosphorus content following incubation, as observed by Kovacs,[27] can only be interpreted as the result of the breakdown of phosphorus-containing organic compounds that are present in the cerebrospinal fluid in those pathologic conditions. When these organically bound phosphorus compounds are acted upon, under incubation temperatures, by certain enzymes, such as phosphatase, liberation of inorganic phosphorus results. This is reflected by a measurable rise in the phosphorus content of the cerebrospinal fluid after incubation, as compared with the preincubation level. As to the origin of the phosphorus-containing organic compounds, it is inconceivable that such large molecules would diffuse from the blood into the cerebrospinal fluid. These compounds must therefore have their origin in the brain substance as result of the breakdown of nerve tissue.

Kovacs'[27] findings thus lend support to the view that elevated cerebrospinal fluid phosphorus in certain pathologic conditions originates from the breakdown of the brain substance. This is especially so in view of the fact that Kovacs' findings of the changes in cerebrospinal fluid inorganic phosphorus values after incubation agree on the whole with our findings of the basic (i. e., without incubation) cerebrospinal fluid phosphorus values in various conditions. Both can, thus, be correlated and integrated on the basis of the above interpretation. In the case of normal cerebrospinal fluid, no breakdown of nerve tissue occurs, and therefore no autolysis of phosphorus-containing organic compounds, which are absent from the cerebrospinal fluid, can take place. The basic phosphorus level is thus normal to begin with, and following incubation no rise in the phosphorus level occurs, as shown by Kovacs. As a result, however, of a destructive factor of whatever nature, whether inflammatory, degenerative, neoplastic, vascular, or other, acting upon the brain substance, phosphorus-containing organic compounds are liberated into the cerebrospinal fluid. Autolysis of these compounds can thus take place, with the result that an elevated cerebrospinal fluid phosphorus will be found without incubation, as our findings indicate, and after incubation a further rise in the cerebrospinal fluid phosphorus will occur, as indicated by Kovacs. This is the case in bacterial meningitis, mumps encephalitis, brain tumor, etc., in which Kovacs' findings would fit in with ours.

There are, however, a number of discrepancies between Kovacs' findings and ours, as in the case with epilepsy and poliomyelitis. Some of these discrepancies can be explained on the basis of differences in the rate of autolysis in the cerebrospinal fluid in various pathologic conditions. This is the case in poliomyelitis, in which the rate can conceivably be very rapid and therefore all the phosphorus-containing organic compounds of the cerebrospinal fluid are broken down very fast, even without incubation. Following incubation no rise in the organic phosphorus can therefore occur, as was actually found by Kovacs. Basically, however, the cerebrospinal fluid phosphorus levels without incubation may be definitely elevated, as was actually found by us and others.[13]

The problem of the origin of the increased phosphorus content of the cerebrospinal fluid in various pathologic conditions of the

central nervous system is of more than theoretical importance. If the view that the cerebrospinal fluid phosphorus becomes elevated as a result of breakdown of nerve tissue is correct, then the elevation of the cerebrospinal fluid inorganic phosphorus may acquire a practical value of great clinical significance. A raised cerebrospinal fluid phosphorus value maintained for a considerable length of time would indicate definite destruction of nerve tissue and a foreboding of neurologic sequelae. On the other hand, normal phosphorus values, or only transitory rises in the course of acute neurologic disturbances, such as head trauma or meningitis, would indicate a favorable prognosis.

This possible correlation, however, between raised cerebrospinal fluid phosphorus values in the course of acute neurologic disturbance and the occurrence of sequelae remains to be evaluated. If such a correlation can be found, it not only would corroborate the destructive origin of the raised phosphorus but would definitely establish cerebrospinal fluid inorganic phosphorus determination as a worth-while procedure of cerebrospinal fluid analysis. In order to establish such a correlation, intensive study of cerebrospinal fluid inorganic phosphorus is required. Such studies are certainly promising to produce very interesting results, and are bound to be rewarding.

SUMMARY AND CONCLUSIONS

The inorganic phosphorus content of cerebrospinal fluid, and its relation to the inorganic phosphorus content of the blood serum were studied by us in 216 specimens, obtained from neurologically normal subjects and from patients with various neurologic conditions. The results obtained are as follows:

1. In the "normal" group, the inorganic phosphorus content of the cerebrospinal fluid averaged 1.6 mg. per 100 cc., with a range of 1.2 to 2.0 mg. per 100 cc. The "normal" group was made up of patients with meningism, febrile convulsions, pulmonary and miliary tuberculosis, mental retardation, and epilepsy.

2. In each of the diagnostic subgroups which made up the "normal" groups no statistically significant deviation of the cerebrospinal fluid phosphorus content was found, as compared with the composite group.

3. Statistically significant elevation of the inorganic phosphorus content of cerebrospinal fluid was found in tuberculous meningitis, purulent meningitis, poliomyelitis, acute encephalitis, and cerebral arteriosclerosis and in specimens removed from neurologically normal patients for spinal anesthesia prior to surgery.

4. An elevated cerebrospinal fluid phosphorus content was also found in isolated cases of cerebral birth injury (recent), cord tumor, compression myelitis, Guillain-Barré syndrome, amyotrophic sclerosis, and multiple sclerosis.

5. No statistically significant elevation of the cerebrospinal fluid phosphorus content was found in syphilis of the central nervous system or in the central nervous system manifestations of chronic alcoholism.

6. No correlation was found between the phosphorus content of the cerebrospinal fluid and that of the blood serum.

7. A definite correlation was found between the inorganic phosphorus content of the cerebrospinal fluid and its protein content.

The fact that elevated cerebrospinal fluid inorganic phosphorus is found in a great variety of neurologic disorders of various origins, not necessarily inflammatory, is in our opinion irrefutable evidence that the elevated phosphorus originates from the breakdown of nerve tissue, which is the only common factor to all these conditions. Further evidence for this view is to be found in recent studies of autolysis in cerebrospinal fluid.

Viewed from this angle, determination of cerebrospinal fluid inorganic phosphorus may possess great clinical significance, particularly from the point of view of prognosis.

Dr. William S. Hoffman, former Director of Biochemistry at the Hektoen Institute for Medical Research of the Cook County Hospital, planned and supervised the laboratory work, and Miss Bernice McNaughton rendered technical assistance.

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Special Article

PSYCHOSOMATIC MEDICINE

Past, Present, and Future

IAGO GALDSTON, M.D., New York

PSYCHOSOMATIC medicine is well on the way to becoming a singular specialty. It now has its coterie of practitioners, its speciality publications, its journals, its monographs, and its historical treatises. True, it is still lacking an international society and a specialty board. But if things move as rapidly and in the same direction during the next 10 years as they have in the past 25, we may expect in the not-too-distant future, both a world-wide society and a specialty board.

These are eventualities which I, for one, do not envisage with pleasure or satisfaction.

Psychosomatic medicine is singular because, unlike all other specialties, it does not revolve about a technological skill, such, for example, as radiology or surgery; or about a definitive system or organs, as is the case, say, with ophthalmology or gastroenterology; or about an age span, as do pediatrics and gerontology. It is not even a nosological specialty, as are those of syphilology, phthisiology, or the neoplasms. Psychosomatic medicine is a singular specialty in that it essentially espouses a distinctive pathological dynamism. It advances the general principle that emotional tensions, chronic or acute, are often discharged in ways that upset the normal physiological equilibrium of an organ, thus initiating the somatic changes that produce disease. Psychosomatic medicine is chiefly concerned with the relationship of emotional tensions to organic and functional disorders.

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A great deal is implicated in this simple statement—vastly more than one is at first likely to appreciate. Indeed, psychosomatic medicine, in its superficial aspects, is all too seductively simple, and hence tends to entice the simple. This is one reason why it is said, and in some instances with warrant, that the psychosomaticists, if I may use that abominable term, among the psychiatrists are suspected of being clinicians, and among the clinicians, of being psychiatrists.

I shall have a good deal to say about the numerous implications of psychosomatic medicine. At this point, however, I want to discuss the recency of psychosomatic medicine. On several occasions, and most recently in my paper on "The Roots of Psychosomatic Medicine," [1] I have argued that psychosomatic medicine is "a strictly modern term," and that "there is nothing in the vernacular of antecedent medicine that can be construed as the homologue of psychosomatic."

These affirmations have been challenged by several colleagues. They contend that in the past many medical authors have employed, if not the precise term psychosomatic, such varied combinations of the terms psyche and soma, mind and body, mental and physical, and in such ways, as to constitute valid equivalents for the term psychosomatic. Margetts [2] has written an illuminating paper on the history of the use of the term psychosomatic, which seemingly gives solid support to those of my colleagues who take issue with me on the recency of psychosomatic medicine.

Nevertheless, I must hold to my judgment. It is indeed true that all of our instructed

and experienced physicians, from the time of Hippocrates down, have appreciated the reciprocal relations of psyche and soma and have employed some conjunction of these terms to designate that relationship. But psychosomatic medicine, as we know and understand it today, as it has been advanced by Alexander, Grinker, French, Stokes, Wittkower, and Halliday, to name but a few, bears about the same relation to the psychosomatic preoccupations of times past as the atom of the "H-bomb" bears to the atom of Democritus. The fact is that psychosomatic medicine, as we know it today, is not a direct-line derivative of the psyche-soma preoccupations of our medical elders, and it profits us little to lump together all the references to psyche and soma to be found in medical history, and to argue therefrom that ours is an ancient preoccupation.

Present-day psychosomatic medicine *is* historically and actually unique. And it is unique in this: that essentially it constitutes a movement to counterbalance and to correct some of the erroneous and corrupting ideas and viewpoints propagated in organicist medicine. However, it must promptly be added that these errors, these corrupting ideas, have so deeply permeated the data and the mentation processes of present-day medicine that even those who are devoted to the study of psychosomatic medicine do not entirely escape them, and are not completely free of them.

To be specific on these scores, psychosomatic medicine *should* be holistic in its orientation and ecological in its embrace. And yet, it is still largely committed to the primitive concept of specific etiology and to the "time and sequence chain of causality," wherein the linkage is a *cause*, emotional tensions which discharge in ways to upset physiological equilibrium, thus initiating somatic changes, and producing disease.

In my paper "Biodynamic Medicine Versus Psychosomatic Medicine," [3] I exposed in some detail the corruptions which psychosomatic medicine has carried over from organicist medicine. I need not, therefore, reargue the issue here. I want, rather, to elaborate the historical antecedents of present-day psychosomatic medicine and to give support to my contention that psychosomatic medicine came into being as a corrective to the faults of organicist medicine.

It is most interesting and very significant that the earliest exponents of psychosomatic medicine were the psychoanalysts. Freud himself was a pioneer in this field. In his "Studies on Hysteria," published in 1895, he reported on the case of Miss Lucy, the English governess in Vienna, whose symptoms turned out to be dependent on the repression of a forbidden attachment to her employer. It was in the discussion of this case, which Freud had treated in 1892, that he first described how the active process of repressing an incompatible idea results in the substitution of a somatic conversion.

This case history is a pristine instance of a psychosomatic disorder, conforming to the now classical definition—"emotional tension discharged in ways that upset normal physiological equilibrium and initiating somatic changes that produce disease." Freud was too busy developing and promoting psychoanalysis to cultivate also the specialty of psychosomatic medicine. That enlisted the interest of a number of his associates and disciples, notably Deutsch, Ferenczi, Groddeck, and Jelliffe. The last-named was without doubt the most ingenious, erudite, imaginative, and inspired pioneer in psychosomatic medicine. Jelliffe had a most comprehensive grasp of all the implications of psychosomatic medicine in relation both to clinical medicine and to psychiatry. Yet I observe with some disappointment that he has received but scant credit for his original and massive contributions to psychosomatic medicine.

I shall have more to say concerning Jelliffe's pioneering work in psychosomatic medicine. Here, I want to revert to Freud's case—Miss Lucy— and to his theory of the conversion of repressed emotional into somatic disorders. This theory was not only original in the highest sense, but also most

revolutionary. It ran afoul of the prevailing schools of thought. It was indeed diametrically opposed and contrary to all the fundamental principles of the biological sciences, then deemed sacred and eternal. What Freud postulated was nothing less startling than that physical changes, that is, demonstrable alterations in the functions and structure of cells, tissues, organs, systems, and of the body entire, could be effected by the psyche. The psyche, be it noted, did not then, and does not now, fit into any of the known categories of "energy and matter."

Here a brief excursion is indicated in order to sharpen our perspectives and to set forth more clearly the originality and profundity of Freud's theory on the conversion of repressed emotions into somatic disorders.

It is an historical fact that many physicians, long before Freud's time, recognized that the psyche in general, and the emotions in particular, affect the operations of the body. The vernacular, in its many and felicitous expressions, such as "eating out one's heart," "can't stomach that fellow," "he gives me a pain in the neck," shows that not alone the learned but the common man as well knew that the soma mirrors the psyche, and vice versa. But the catch had always been in the how of the trick. *How* does the soma affect the psyche, or the psyche the soma? It is simple enough to perceive that they are ligated: The challenge lies in establishing the *nature* and the *dynamics* of that ligature.* Freud's merit and originality lie precisely in this, that he was not content merely to affirm that psyche and soma are ligated, but went further and postulated a theory to describe and to account for the ways by which, and because of which, the psyche affects the soma—and produces disease. That was his theory of repression. This theory he elaborated to embrace the two-way relationship of psyche-soma and soma-psyche.

Freud considered the syndrome he labeled anxiety neurosis to be the somatic witness of a "psychic repression," while hysteria he held to be the psychic witness of a "somatic repression." [4] This is Freud's elaboration of this theory:

> In each of them [that is both in anxiety neurosis and in hysteria], there occurs a deflection of excitation to the somatic field instead of psychical assimilation of it: the difference is . . . this, that in anxiety-neurosis the excitation is purely somatic, whereas in hysteria it is purely psychical.

It is not relevant to our purpose to establish whether Freud's postulates are correct or not, nor does it matter whether we do or do not accept them as such. It is, however, pertinent that we fully appreciate the fact that in this theory Freud argues that the psyche affects the soma through purely psychological means.

This is a rather bold statement, which I permit myself only in the interest of emphasis and clarity. It suffers the fault of historical foreshortening or condensation and distorts the actuality. What I mean is that at the time Freud first advanced his theory of repression he himself was not too clear, or certain in his mind, that repression *was* purely a psychological operation. He entertained the idea that possibly repression might in effect operate through some toxic chemical agent which it engendered, or liberated.

All this may seem like so much trivia. But it is really quite significant and is relevant to the very core of our concern. For we need to bear in mind that at the time Freud made his pronouncements, the psyche, qua psyche, was officially nonexistent. Purely psychological forces were held to be inconceivable, and hence nonexistent, and he who played with such ideas was deemed to be either an ignoramus or a charlatan, and, most likely, a good deal of both at one and the same time. We need also to appreciate that neither Mesmer, nor Braid, nor Bernheim, nor Charcot, nor Janet, these being among the outstanding men to concern themselves with hypnoses, hysteria, and neurasthenia, postulated in their various theories the operation of purely psychologi-

* If I mistake not, that is at the root of Hans Selye's researches today, and I know that Harold Wolff and his associates, as well as Grinker, French, Alexander, and their associates, have been and are working intensively in the exploration and on the illumination of just this problem.

cal forces or mechanisms. They did conceive of subtle agents, such as immaterial fluidisms, animal magnetism, suggestion, neurasthenia, and so on. But these were not psychological dynamisms, as Freud's repression was.

In this connection, it will profit us to recall the conflict between the schools of Nancy and that of the Salpêtrière. In the latter, Charcot demonstrated to his own satisfaction the existence of a "fluidium," for he was able, by means of large magnets, to transpose disturbances, such as paresthesias, contractures, and paralysis, from one side of the patient's body to the opposite side, or from some proximate to some remote part of the body. The Nancy school, however, discredited these demonstrations, for they proved that Charcot's patients were "trained performers," reacting exactly as was expected of them—and that the magnets were inconsequential, for a pencil in the hand of the hypnotist would prove just as effective if the patient but thought it was a magnet. Bernheim, the leader of the Nancy school, ascribed Charcot's, as well as his own, hypnotic influences to suggestion. Suggestion he described as the manifest influence of an extraneous idea (that of the hypnotist) on the brain, and hence on the behavior of the person who accepted the idea. According to Bernheim, suggestion though psychological in nature, operated as an exogenous force.

Freud, oddly enough, sided with Charcot against Bernheim. He had translated the works of both. This ambivalence, which is both interesting and significant, can be accounted for by the atmosphere in which he grew up. His psychiatric preceptor, Meynert, was an out-and-out organicist, and Brücke, the teacher who had made the biggest impression on Freud, was a partisan of that school of thought, elaborated by Helmholtz, DuBois-Reymond, and Ludwig, which militantly maintained that all vital phenomena, no matter how complex, and including also the mental and psychological, are ultimately explicable in terms of physics and chemistry. Brücke's teachings were Freud's point of departure in the elaboration of his psychoanalytic theories. But he did not follow them for long. The so-called "toxicological" theory of neuroses which Freud initially propounded he ultimately abandoned, and repression in the Freudian system acquired a pure and unadulterated psychological character.

I have gone to some lengths in elaborating the history of Freud's excursion into the field of psychosomatic medicine for two reasons—first, to celebrate his pioneering contribution, and, second, to highlight the difficulties he experienced in freeing his own thinking of the materialist, organicist patterns which conditioned, and currently still hamper, so much of medical and biological comprehension and understanding. Also, my scruples as a medical historian would not allow me to gloss over the obscurities and paradoxes inherent in Freud's initial exposition. And while speaking in the guise of a medical historian, I think it of interest to point out that it was the Russian physiologist Pavlov who first demonstrated the purely psychological nature of the neuroses, albeit experimental, in his case. This field of study has been brilliantly and most profitably developed by a number of American workers, including Horsley Gantt, Jules Masserman, and Howard Liddell.

To revert now to the main stream of our exposition: I had observed that the psychoanalysts were among the very earliest workers in psychosomatic medicine. It was they who postulated that disturbances in the psyche could, and frequently do, become manifest in somatic disorders. Initially this postulation was advanced as a protest to the prevailing organicist-mechanistic concept of the etiology of disease, a concept which held chemical-physical changes in the material structure of the body the essential antecedent to all manifest pathology. With time, however, the protest became *ein Ding an sich selbst*. It became, in other words, psychosomatic medicine. Now it was no longer just a protest; not merely the affirmation that hysteria, with all its protean symptoms and disorders, was not due to a "wandering of the womb," to animal magnetism, to hereditary debility, to some malign fluidium, etc., but was due, rather, to a purely

psychological mechanism labeled by Freud "repression." Now indeed the initiative was with the psychiatrists, and they premised that a host of disorders, ranging from Dupuytren's contractures to psoriasis, were psychogenic in origin, or at least showed "evidence of being related to psychological stress." The list has grown with time, and currently it includes such morbidities as infantile cachexia, hyperinsulinism, diabetes, gout, hyperthyroidism, glaucoma, keratitis, asthma, hay fever, sinusitis, headache, peptic ulcer, ulcerative colitis, constipation and diarrhea, arthritis, backache, angina pectoris, hypertension, neurocirculatory asthenia, impotence, dysmenorrhea, hives, and eczema. This catalogue, compiled by Stanley Cobb, was drawn from a recent publication of the Association for Research in Nervous and Mental Disease.[5]

In this array of disorders, it is maintained, not chemical and physical, but rather psychological, factors play the determinant etiological role. Thus has the Helmholtzean position been challenged: There seemingly is much more to life and to life's processes than chemistry and physics. There is also psychology.

So far so good. But when we look closer into the matter, we perceive that the victor has introjected the vanquished; or, to phrase it more simply, that psychosomatic medicine has incorporated within its own formulations some of the distorting concepts of organicist medicine. These, to name them promptly, are the error of specificity and the error of time-sequential causality. Let me hasten to make clear just what I have in mind. First, as to specificity. Organicist medicine has long maintained that every disease must have its specific causative factor: the tubercle bacillus in tuberculosis; the Pneumococcus in pneumonia; hypoinsulinism in diabetes, and so on. Psychosomatic medicine has seemingly not challenged this postulate. It has merely added a new morbific factor—the psyche, or, more specifically, emotional tension, frustrated drives, repression. Psychosomatic medicine, quite in line with organicist medicine, is patently that department of medicine which specializes in the psychogenesis of organic disease. It is concerned with the psyche as a morbific agent. Bunker has phrased it thus:[6]

> The key question involved might be said to be that of "psychogenesis." That is, can psychological factors give rise to "organic" disease? May they have a place in the chain of causative events which lead to "organic" disease? If so to what extent is this true, and what are the psychological factors thus involved?

The second gross error which psychosomatic medicine has incorporated is the fallacy common to all of etiological medicine. It is the fallacy of time-sequence causality. This formulation maintains that in a determinable time sequence it can be observed that factor A causes the eventuation of B, which, in turn, causes the eventuation of C, and so on—"till death puts an end to it all." Stanley Cobb has tersely phrased this issue: "One of the main tasks of psychosomatic medicine . . . is to study the sequence of events from stimulus to symptom." † This is proximate to Bunker's "key question," cited before, namely the *position* of the psychological factors in the chain of causative events which lead to organic disease. According to Cobb, the position of the psychological factor is quite certain; the sequence of events is "from stimulus to symptom." The differential contrast between the organicist and the psychosomaticist thus becomes crystal-clear. For the organicist the somatic event precedes the psychological, or, as I recently heard it so aptly phrased, and with such enviable assurance, "the spirochetal infection is the inevitable and invariable forerunner of dementia paralytica." How blessedly peaceful it must be never to be troubled by such galling questions as to why the case in mind cohabited with infection, or why he did not apply prophylaxis, or adequate treatment to the syphilitic infection—in other words, never to be troubled

† Miles, Cobb, and Shands,[5] p. 18.

by the psychological potential that must have anteceded the materialized event.

For the psychosomaticist, on the contrary, the psychological event precedes the somatic. The stimulus leads to the symptom.

Evidently, then, the time-sequence causality chain, as postulated in psychosomatic medicine, is but the mirror image of that postulated in organicist medicine. Thus, the evil has not been corrected; it has only been multiplied. And as long as it prevails, the conception of the "essence of psychosomatic medicine" as "the cooperation of practioners of medicine, surgery, dermatology, etc., with psychiatrists—each doing his part and together helping the patient" (Cobb‡ is neither encouraging nor promising. We have seen in other connections that the cooperation of specialists does not per se or per force, serve the best interests of the patient. In the absence of competence in comprehension, the opposite is more commonly the case. The patient, as an entity, is more likely to be overlooked and lost, the more numerous the cooperating specialists.

I cannot terminate the exposition of this part of my argument without bringing in witness Franz Alexander's labored efforts to deal with the incorporated faults which psychosomatic medicine has carried over from organicist medicine. In his definitive work "Psychosomatic Medicine,"[7] we find the following categorical statements:

> With the recognition that in functional disturbances emotional factors are of causal significance, psychotherapy gained a legitimate entrance into medicine proper and could no longer be restricted exclusively to the field of psychiatry. . . .§ Formerly every disturbed function was explained as the *result* of disturbed structure. Now another [sic] causal sequence has been established: disturbed functions as the cause of altered structure.‖

The last is an unequivocal and a pertinent statement bearing on what I have termed the morbific potentials of the psyche and the mirror image of time-sequence causality. Alexander later reaffirms these views in the statement:

> The resistance to this concept is based on the erroneous dogma that disturbed function is *always* the result of disturbed structure and on a disregard of the reverse causal sequence.¶

By the witness of these citations, it would appear that Alexander was unaware of and insensitive to the problems involved in "specificity" and of "causality." However, that such is not entirely the case is to be seen from the following citations:

> The term "psychosomatic" should be used to indicate a method of approach both in research and in therapy of somatic . . . methods and concepts on the one hand and psychological methods and concepts on the other. . . . Emphasis is placed upon the qualification "coordinate use," indicating that the two methods are applied in the conceptual framework of causal sequences.#

The obscurity of these sentences, wherein a plea is made for the simultaneous coordinate use of data in the conceptual framework of causal sequences, shows that Alexander is impaled upon the horns of a dilemma. On the one hand, he subscribes to the scheme of causal sequences; on the other, he would qualify psychosomatic medicine as a method of approach, distinguished by the simultaneous and coordinate use of data.

The time now has come to ask, What does all this add up to? Criticism is legitimate enough an exercise, but it is more grateful when it is, as they say, constructive. Unless one can perceive "a way out," expositional argumentation is bound to be anxiety-provoking, and at times exasperating. What, then, is the summation of the argument? What's to be done?

Actually the challenge facing us is clearly evident, and simple to formulate. We need to free ourselves of the naïve 19th century concepts of specificity and time-sequence causality. We need to pay more than nodding respect to the concept of holism and to the vision of man operating in an ecological setting. We need to eliminate from our think-

‡Miles, Cobb, and Shands,[5] p. 3.

§ Alexander,[7] p. 43.

‖ Alexander,[7] p. 45.

¶ Alexander,[7] p. 46.

Alexander,[7] p. 50.

ing the concept of a causality relationship between psyche and soma.

Instead of reasoning that a patient develops a peptic ulcer *because* of emotional tensions, we need to understand that the given patient represents a dynamic aggregate, that he is affected by forces which alter his dynamic configuration, and that we witness such alterations in the totality of his being and in all of its relations. Similarly, instead of conceiving the sick person as having regressed to a lower personality level *because* of his illness, we need, rather, to understand that the interplay of forces which "makes" the patient sick, also, and at the same time, though possibly in different manifest degrees, effects that alteration in personality which we label regressive.

Medicine must needs become that science which studies the living organism, itself a dynamism, as it moves and is affected by the surrounding forces and continuously alters its own *and* the surrounding configurations. Force, in the patterns of matter and energy, has a common and basic character; yet in experience it is manifest in many guises—physical, chemical, thermal, electrical, psychological, and social. There are numerous distinguishable embodiments of force, and their dynamic effects upon the human organism are well known. These include such instances as parasites, bacteria, toxins, inorganic poisons, physical agents with high momentum, extremes in temperatures, etc. Some forces—for example, suggestion, ideals, panic—operate without corporeal embodiment.

The significant idea, then, is that the living organism conceived as a dynamism is continuously exposed to the effects of the multiform forces which surround it. The destiny of the organism, and its temporal configuration, is affected and determined by the very modifications it experiences, as a result of the interaction of its own dynamism with the surrounding forces.

I have several times endeavored to illustrate this somewhat intricate concept by means of some analogical picture. The one that has served me best is that of a spinning top. There is a certain kind of top which carries on its upper surface a number of small discs of different colors. These discs are so geared to each other and to the top itself that, as the latter spins, the discs revolve and effect a continuous change in colors and hues. In this contraption the relation of the position of the colored discs to each other and the colors to be seen on the spinning top change simultaneously. The point to underscore here is that the colors do not change *because* of the change in the relations of the discs to one another. It is, rather, thus: The discs change *and* the colors change. A time sequence between the change in the position of the discs and in that of the colors is inconceivable; also, there is no causality relation between the one and the other.

You will, I am sure, recognize that what I have elaborated here is an instance of ecological relations. In this connection, I want to revert to Smith Ely Jelliffe, who, I believe, better than any of the pioneers in this field grasped and understood the essentially ecological nature of psychosomatic medicine. Jelliffe was a prolific writer, and almost everything he wrote, whether it be on botany, on paleopsychology, or on the drama, affords profitable reading. From his many papers, I would commend two especially.* These papers do not spell out the principles of ecological medicine in full detail. But you will find therein the *Anlage*, the germinal thoughts, the ideas, and the vision of ecological medicine, related particularly to psychosomatic problems. Let me cite but two brief passages.[9]

"Any deviation," wrote Jelliffe, "from object or aim threatens the harmonious action patterns within the machine."† And in elaboration of this somewhat cryptic dictum, Jelliffe wrote:

> When we refuse to get in line with nature, as registered in the faulty purposes of life, i. e., our mental states, even the kidneys, the blood pressure and urea, proteid, ionic milieu become involved and this is but one formula for many disease.[9]

* References 8 and 9.

† Jelliffe,[9] p. 583.

Many excellent research workers have labored, and are now laboring, to lay bare the "mechanisms" of psychosomatic disorders, and their labors have yielded good results. To the migraine sufferer it is no small matter that the attack can now be effectively aborted. It is ever of value to be able to intrude upon and effectively to interrupt and to amend the pathological processes operating in disease. But such interruptions, even when they succeed in removing the symptom, seldom correct the disease. In contrast to the many clinical and research efforts put forth, to lay bare the mechanisms of psychosomatic disorders, few have, or are, laboring where Jelliffe first broke ground; that is, in the effort to orient the viewpoint and understanding of psychosomatic medicine holistically and ecologically.

So far as I am able to judge, Halliday, in England, and Grinker, in the United States, are the only ones to have cultivated this terrain with any intensity and perseverance. Halliday's excellent book[10] is holistic in viewpoint and ecologically oriented. Grinker's "Psychosomatic Research"[11] is a *capo lavoro*: a splendid exposition of the problems I have in part belabored here. I myself, in a much more modest way, have worked in this field, as witness my work "Social Medicine."[12] I would be remiss did I not mention in these associations the work "Recent Developments in Psychosomatic Medicine,"[13] published under the editorship of our distinguished colleague Dr. Wittkower.

Having pointed out the task before us, which is to reorient our thinking radically, I am moved to phrase the question, which I believe must be in your minds. "How will all this profit us, and our patients?" Does it really matter whether we think as organicists or as ecologists, and whether we do or do not understand "the chain of causality?" Let us assume that we could bring relief to the migraine victims, to the asthmatic, to the hypertensive, to the ulcer or colitis sufferer; would not that suffice for them, and for us, too?

It probably would! But here there comes to the fore the range of one's vision, the embrace of one's understanding, and the magnitude of one's ambition to contribute to our science and to the ultimate good of people. It is a matter also of being intelligent and of anticipating the future.

The current ideological orientation of medicine as a whole, psychosomatic medicine included, will not do, for it does not meet the long-term needs either of the individual or of society.

In my paper "The Roots of Psychosomatic Medicine," I called attention to the fact that psychosomatic medicine drew its momentum not from psychoanalytic insight but from epidemiological necessity. Since the beginning of this century demographic disease patterns have changed remarkably. The infectious diseases have receded both numerically and in importance, while the functional and degenerative disorders have come to the fore. These last categories embrace many instances of psychosomatic disorders; indeed, I would venture the guess, for there are no dependable statistics on these scores, that the psychosomatic disorders outnumber all others.

The overwhelming question thus arises: How are we to serve these people? That indeed is the ultimate issue.

Candor obliges us to admit that the greater numbers are not served at all—at least not beyond the casual diagnoses of their immediate and superficial complaints, and the delivery of "a prescription for what ails them." Witness in this connection, on the one hand, our enormous consumption of anodynes, sedatives, analgesics, and other "pain and worry killers," and, on the other hand, that of the "picker-uppers," such as the amphetamines.

But on this occasion I am more concerned with the so-called psychosomatic patient than with the larger numbers that are not served at all, or that are treated superficially, that is, symptomatically. The psychosomatic patient is all too often shuttled between clinician and psychiatrist. Generally, when the clinician comes to the end of his rope, he refers the case to the psychiatrist. The psychiatrist, of

course, seldom refers his patients to anyone. A dermatologist, after a frustrating four-year tussle with an eczematous young man, referred him to me. Naturally, the young man wanted to be treated for his skin disorder. He did not quite grasp what I meant when I said I would be glad to treat *him*, but not his skin. However, my prize case was a young tuberculous woman, referred by an internist, with a unilateral pneumothorax, who suffered also from depression, anorexia nervosa, and mild paranoid ideas.

Cooperation of psychiatric and nonpsychiatric specialists in diagnosis and treatment of the psychosomatic patient is postulated as the high desideratum both by Alexander and by Cobb. Such cooperation is a widely fostered ideal in psychosomatic circles. It is, however, at best an ideal which is workable and feasible only in institutional settings. I am not even sure it is an ideal. I suspect that specialists are here to be employed, that is used, rather than to be cooperated with. One operates, rather than cooperates, with a tool or instrument. What I have in mind is this. By definition all psychosomatic issues are both clinical and psychological. But they are seldom equipotentially both. In reality and for effectiveness, one or the other must carry responsibility, the clinician or the psychiatrist. The other's services might be utilized in an interim. But the case must be treated within a definitive *Gestalt*. For this reason I cite, but do not subscribe to, Alexander's division of specialists into psychiatric and nonpsychiatric: At least I do not contemplate with satisfaction the existence of any specialty so devoid of psychiatric knowledge and insight as to warrant such designation. What I rather conceive of is the clinician, or general practitioner who, if you please, is so well indoctrinated psychiatrically that he is able to treat his own case competently, that is, with a full awareness of the psychologic components of both the patient's pathology and his therapy. Such a clinician, even when dealing with the so-called psychosomatic case, and what case is not such in some measure at least, is not likely to require the cooperation of the psychiatrist, except consultatively. If and when the patient's difficulties become predominantly psychological, he will, of course, be referred to the psychiatrist. Obviously, it is not expected that the clinician will also be a psychiatrist. Similarly, it is not expected that the psychiatrist will function also as a clinician. But it is to be expected that the psychiatrist will possess and will exercise more clinical acumen and awareness than is commonly the case today. Except for our institutional confreres, and a small group of psychologically oriented practitioners, psychiatrists in the main, and orthodox Freudians notably, seem to look upon the body as an appendage of the psyche, and hence they trouble little about it, at least clinically. All this might perhaps be phrased more charitably by saying that the psychiatrists appear to operate in the firm conviction that when all goes well with the psyche, all will be well with the soma.

I must dwell a bit longer on these scores to make sure that my point is clearly made. I hold that the clinician, contemplating the patient in the soma-psyche perspective, and the psychiatrist, in the psyche-soma perspective, each views the patient in a distorting tangent. I hold, further, that when you add up what they respectively perceive you thereby acquire, not a better picture of the patient, but, rather, a more distorted one. I submit that no view corresponds to the reality but the holistic and the ecological. I maintain that both the clinican and the psychiatrist, even when functioning in their separate fields, can operate holistically and ecologically. Their functions, however, are essentially disparate, for, even though psyche and soma are invariably involved and affected in health and disease, in the practical experience of man the case is generally "either-or."

Finally, I am persuaded that the historical function of the psychosomatic movement is not to add another to our Babel of specialties but, rather, to vitalize the whole of medicine, psychiatry no less than clinical medicine, with the holistic and ecological viewpoint. When that has been achieved, the psychosomatic

movement will have fulfilled its mission and it will have been absorbed into medicine.

2 E. 103d St. (29).

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Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY; NEW YORK NEUROLOGICAL SOCIETY, AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, April 21, 1955

Axel K. Olsen, M.D., *President, Philadelphia Neurological Society* and
E. Jefferson Browder, M.D., *President, New York Neurological Society, Presiding*

Observations on Illusory Awareness of Bodily Parts. Dr. Samuel Brock, New York, and Dr. Harold Merwarth, Brooklyn.

Three cases which illustrate remarkable abnormalities in body-image perception were presented. (Because of limitation of space, only one case is reported here.)

Case 1 is that of a very intelligent electrical engineer, holding a position of importance. He had had hypertension for many years, the pressure averaging about 180/110. On July 1, 1950, he developed a variety of oculomotor and other cranial nerve signs with ataxia, pointing to a brain stem lesion of thrombotic nature, involving a branch of the basilar artery. After some improvement there was a serious exacerbation in mid-September. Beside the considerable involvement of the cranial nerve innervations, there were marked left hemiparesis and ataxia and severe left hemianesthesia, with particular emphasis on the loss of proprioception. About the same time he developed the belief that the left arm did not belong to him, and at times he thought that it belonged to his daughter. This finally gave way to the "feeling" that there was a parasitic left hand and a foreshortened forearm springing from the real forearm. These phenomenon were associated with a great feeling of coldness in both the real and the spurious member. These body-image disturbances fluctuated a good deal, became less evident as time went on, and disappeared altogether in the spring of 1951. All laboratory data were negative, including the EEG. X-ray studies of the skull and spinal puncture were not done.

There seems little doubt about the gross anatomic diagnosis, namely, vascular lesions in the brain stem, particularly on the right side. There are a number of interesting points in this case: (1) the patient's clear mentality and insight into the illusory nature of his parasitic hand, and the illusory posturing of the left upper and lower limbs at times; (2) the earlier attribution of the left limb to someone else, this phenomenon disappearing, to be followed by the development of the parasitic part; (3) the cutting off of almost all sensation from the affected left limb and left side, with the feeling of intense cold in the left "hand," i. e., the natural, as well as the parasitic, hand on the left; (4) the absence of any confusion on either side or of aphasia or obvious apraxia; (5) the lack of any evidence of cerebral cortical disease; (6) the disappearance of the illusory awareness of the parasitic hand.

DISCUSSION

Dr. Gabriel A. Schwarz, Philadelphia: In a review of the three case histories, certain things stand out as deserving further discussion. In the first place, the laterality of the lesion is important. In the second case the lesion was in the left cerebral hemisphere, which I presume was the dominant, or major, hemisphere. The first and third cases suggested a lesion in the minor cerebral hemisphere. The literature to date has stressed the fact that disturbances in body image occur in the side opposite the minor hemisphere. Such a lesion is usually in the parietal lobe.

I should like to ask the authors the following questions: In their first case, while the lesion seemed to involve the brain stem, is it possible that a branch of the the posterior cerebral artery may have been involved, with subsequent damage to the thalamoparietal bundle, and yet have given no evidence by electrocephalogram of its presence?

In the second case, do the authors have any explanation for the phenomenon of incorporation occurring bilaterally when the lesion was unilateral, in the left cerebral hemisphere?

In the third case, could the patient be made to recognize his left limbs as his own by feeling them with his right hand? Also, in this case, did the patient recognize both sides of the examiners themselves, since he had such a tremendous splitting of the extra-body-hearing sphere?

DR. ROBERT JAFFE, New York: In contrast to some of Dr. Brock's material, all the cases in our series who showed disturbance of body image or had difficulty in the appreciation of space had general disorientation. All the patients showed some disturbance in visual function, and most showed some defects in somatic sensation, although perhaps only minimal disturbances in adaptation time, or disturbance in shape perception with bilateral stimulation.

DR. HAROLD R. MERWARTH, Brooklyn: There is little mention of the condition in the neurologic literature. I took occasion to investigate this question in the recent neurologic textbooks and examined 10 of them. In three, anosognosia is not even mentioned. In others, the authors cite specific localizations. For instance, Nielsen places it in the connections between the thalamus and the supramarginal gyrus. In the very recent, three-volume "Clinical Neurology," edited by A. B. Baker, Foster states positively that the lesion occurs in Area 40; Purves-Stewart places the defect in the thalamus. Russell Brain localized it to the supramarginal gyrus. It is discussed by Russell Brain and Wechsler and in the recent three-volume edition of Wilson. It is mentioned by deJong and in the 1911 edition of Oppenheim's text. As you can readily see, there is a wide fluctuation of opinion as to the nature of the condition and a possible anatomic site.

We know more about the anatomic involvement in the first case than in the others: This patient had a marked disturbance to cold; he could hardly tolerate it. We do see a disturbance of this type in spinothalamic involvement in other parts of the nervous system—for instance, in the spinal cord and in the brain stem, too. We believe there was no evidence to suggest a cortical involvement. There was no hypersensitiveness to pinprick, as we see in thalamic lesion with hemiplegia dolorosa.

In regard to the question whether his proprioceptive sensation had returned prior to the return of motor function, I would like to stress the point which Dr. Brock made, and put it very clearly, viz., that this was almost essentially a sensory hemiplegia; there was motor involvement, but very little. All modalities of sensation—pain, temperature—were involved. The proprioceptive modalities never did return, while pain appreciation returned in spots.

The other question, regarding the phenomenon of incorporation of the extremities: That seems to be a psychological hazard. I am inclined to feel that it may be a carry-over of the so-called Gerstmann phenomenon (a projection, so to speak): the inability of the patient to recognize the examiner's fingers as not his own.

DR. SAMUEL BROCK, New York: I want to emphasize what Dr. Schwarz has pointed out, i. e., that a sensory component may have been an important factor in producing this curious syndrome in our Case 1. I would like to make it clear that in this case the man's marked loss of proprioception persisted even though the parasitic hand finally disappeared. It might be argued that our second case exhibited a Gerstmann syndrome of some degree; the finger agnosia present on her first examination was almost gone at the second examination, a short time later. She never showed any other change in her own body image. Just how the Gerstmann syndrome is to be correlated with her falsity of identification of the fingers of others placed in her palm, I do not know.

I should like to make the point that our first patient was a very clear, intelligent, and cooperative person who had no psychotic manifestations whatsoever and to emphasize that Cases 1 and 2 had no denial of illness. In Case 1 the man made up his mind that the parasitic hand was a neurotic manifestation, and so he would attempt to "brush it off," while still feeling all his incapacities, from a mild motor and a marked sensory defect on the left side; Case 2 continued to be upset by her illness, which she knew affected her brain.

The Eye-Centering System. DR. MORRIS B. BENDER, New York.

This paper was published in the June, 1955, issue of the ARCHIVES, page 685.

DISCUSSION

DR. ERNEST A. SPIEGEL, Philadelphia: I was very much interested in following these experimental and clinical studies by Dr. Bender and was greatly impressed by all the clinical observations and experimental data on which he bases his theory. The cardinal problem seems to me the relationship of the centering system to the deviational system—whether we are dealing with two anatomically distinct systems or with various functional states of one and the same system, depending on the state of excitation of the higher centers, the state of the peripheral neurones, and the parameters of stimulation. At the present time it seems to me

hardly possible to decide these questions definitely; even if further studies show that a unitarian view should be accepted, it seems to me that Dr. Bender's hypothesis has led him to very important observations. I personally am particularly interested in the mechanism of vestibular nystagmus, and I should like to illustrate this problem by a few examples. If we elicit vestibular nystagmus with the eye originally in the central position, the labyrinthine component deviates the eyes upward or downward, and then a fast component in the opposite direction is superimposed. However, it never brings the eyes back to the central position; they remain in a deviated position. Another case is the rotational nystagmus; here we deal with a clockwise movement in one component and a counterclockwise one in the other component, or vice versa, but there is no centering in any component; any theory of nystagmus should, of course, explain all types of vestibular nystagmus.

A third example, which is not so rare, appears if a patient looks in the direction of the fast component. For instance, a nystagmus is elicited by cold-water irrigation of the left ear and the patient looks to the right side. In this way a nystagmus is produced to the right, with the fast component to the right and the slow component to the left. We have here an example in which the fast component is away from the center and the slow component is toward the center; in other words, we can hardly explain such a case by assuming that the fast component is identical with the centering system. It seems to me that Dr. Bender has devised a very ingenious theory, and I am sure he will continue to shed more light on many obscure neuro-ophthalmologic problems.

Dr. Nathan S. Schlezinger, Philadelphia: In his presentation, Dr. Bender has again demonstrated his keen interest in many of the problems that have long confronted the neurologist and ophthalmologist. The experimental observations concerning midposition or eye-centering mechanisms, which he and his co-workers have described since 1948, have certainly been thought-provoking from a clinical standpoint.

When we study the development of fixation reflexes, it may be worth while to consider whether the eye-centering system is a purely subcortical, involuntary reflex mechanism or whether it is a cortical, and at least partially voluntary, mechanism.

Does Dr. Bender have any ideas relating to the problem of concomitant strabismus and the various phorias and tropias?

With regard to optokinetic nystagmus, I find it difficult to follow the correlation between the quick component and the eye-centering system, since the experimental observation has been described as a slow rolling motion.

Dr. Melvin Thorner, Philadelphia: I should like to submit that there is in man an eye-centering system which is quite independent of the existence of a nervous system. It is a mechanical system, due to the elasticity of the capsule of Tenon and other orbital structures. If this be so, eye centering may then be accomplished either by this neurologically passive mechanism or by the active and appropriate contraction of the extraocular muscles. To discriminate between the two, one would require action potential records either from the extraocular muscles or from the third, fourth, and sixth cranial nerve complex. It may be that stimulation of a cerebral area, resulting in eye centering, is due merely to widespread inhibition of the nuclei of the third, fourth, and sixth cranial nerves. In this case such stimulation merely sets the stage for a purely mechanical centering of the eyes to their position of rest.

Dr. Morris Bender, New York: I want to thank the discussors, and I must say I cannot answer many of their questions. I said that I was presenting theory. We are using this hypothesis to investigate the neuroanatomic basis for eye movements, and we have thought of the questions put by Drs. Spiegel, Schlezinger, and Thorner.

I want to make one comment about vestibular nystagmus. The fact that the nystagmus is increased in the direction of gaze does not necessarily detract from the concept that the eyes tend to come back to their original position. If the term "center" is not accurate, one may use "original position" or "midposition."

In reply to the question concerning optokinetic nystagmus: There is a quick component which returns toward the center and a slow deviational one which follows the stripes. The eye-centering mechanism corresponds to the quick component.

As for Dr. Thorner's question: We are well aware that the eye centering might be a complete relaxation of eye movement. It is suspected that in many conditions the centering

movement is an inhibitory effect, but there are instances in which the centering is an excitatory act. We think that eye centering is the result of a combination of excitation and inhibition.

Total Removal of Acoustic Nerve Tumors. Dr. J. Lawrence Pool and Dr. Arthur A. Pava, New York.

Total removal of an acoustic nerve tumor is the procedure of choice if it can be safely done, for, according to the literature, it removes a 50% chance of recurrence within three to five years, which, in turn, carries a 25% to 60% risk of fatality after a second or third operation. Total removal (author's series) also restores nearly 80% of the patients so treated to a useful capacity in life, a percentage which is better than that for subtotal removals.

Preoperative contraindications to total removal include cerebral arteriosclerosis, vascular hypertension, myocardial damage, gastric or duodenal ulcer, or debilitation. Operative contraindications to total removal in one stage are extreme central or midline extension of a large tumor and excessive vascularity or adherence of the tumor at the site of its contiguity to the brain stem. Careful study of these cases also suggests that a significant, though temporary, failure of vital signs before or during the operative removal of tumor tissue is often a bad prognostic sign, which should warn the surgeon against total removal. Total removal, of necessity, implies the threat of facial nerve palsy, owing to the fact that the tumor nodules within the internal auditory meatus must be removed, making it difficult generally to save this nerve. However, facial-hypoglossal nerve anastomoses almost always restores effective voluntary control to the paralyzed side of the face.

Altogether, then, each case must be carefully considered not only before, but again at the time of, operation, so that everything possible may be done to preserve the life and functions of the patient harboring this most difficult of all brain tumors. In a word, while total removal is clearly the procedure of choice, it should not be attempted in the presence of any of the contraindications just described.

DISCUSSION

Dr. Francis Grant, Philadelphia: The removal of an angle tumor is the most difficult operation in neurosurgery. If you can take an angle tumor out, you can feel you are a good neurosurgeon. The problem, I think, is just about as Dr. Pool stated. Some of these tumors can be extirpated, and some cannot. The tendency most of the time, I have found, it to try to do a little bit too much.

I am frank to admit I have never saved the facial nerve. Olivecrona says he can, and Dr. Pool says he can; so I should be able to, but I must say I never have. Postoperatively, hypoglossal-facial anastomosis will give a satisfactory result. My feeling is that the sacrifice of the facial nerve is rather a cheap price to pay for the complete removal of an angle tumor.

Dr. Rudolph Jaeger, Philadelphia: I have adhered to the surgical philosophy of total removal of cerebellopontile tumors, and I do not at present recall any instances of subtotal or intracapsular removal of these tumors. In several instances I must have left tumor tissue where it had eroded deeply into the temporal bone through the internal acoustic meatus. However, I cannot remember a second operation in such a case.

The facial nerve has, in my recollection, seldom been saved. I recall recently total removal of bilateral tumors of considerable size with complete preservation of this nerve on one side. Spinofacial anastomosis has always been performed for correction of the facial paralysis. A motion picture shows the movement of the face following spinofacial anastomosis.

Prof. Norman Dott, Edinburgh, Scotland: I would like, first, to bring to you greetings from the neurologists of Europe. As you know, we are watching over there, with the greatest interest and admiration, the advances that are made here, and we gain great inspiration from them. Many of you over here know my personal debts to Harvey Cushing many years ago; and I should like to thank you very much, as a vagrant neurologist for the moment, for your hospitality in allowing me to attend this meeting. I have listened with great interest to the papers. In respect to the last paper by Dr. Pool, which I am invited to discuss, I would say that in Britain we agree entirely with his general attitude toward these tumors. It occurred to me that I might mention three relevant matters. Dr. Pool pointed out the difficulty of carrying out the ideal operation of complete removal in patients who showed some stability before operation. I think that to some extent we have been able to meet that situation by draining the ventricles externally for several days before such an operation, by frontally inserted catheters.

My second point is that I observed with the greatest admiration the results of the spinofacial and hypoglossal-facial anastomoses. We have followed your example there. I have had five occasions to repair the facial nerve somewhat more directly in removing an acoustic tumor. At times the facial nerve can be quite clearly seen, and, in the interest of complete removal, it may be deliberately cut across and the tumor completely removed. In this circumstance one can apply nerve grafting. The graft is sutured to the stump of the severed facial nerve close to the brain stem, brought out through the cerebellar access, pushed forward under the sternocleidomastoid muscle, and then some 90 days later, when the growing fibers are nearing the lower end of the graft, the second suture is made at the back of the parotid gland, anastomosing the graft to the distal part of the facial nerve.

Dr. Jaeger asked about the 12th-nerve versus the spinal-accessory-nerve anastomosis. Some years ago, Dr. Stookey, in his book on "Peripheral Nerve Surgery," went extensively, on theoretical and practical grounds, into the theory of why hypoglossal nerve anastomosis is more successful. The hypoglossal nerve is linked with the cortical mechanism for speech through voluntary face and mouth motion much more closely than is the cortical representation of the spinal accessory nerve.

In reply to Professor Dott, I have drained the ventricles preoperatively in one case, with great success as to ease of total removal of the tumor, followed by a complete recovery. We should undoubtedly do this oftener.

Hydrocephalus Associated with Lipoidosis of the Central Nervous System. Dr. Stanley M. Aronson and Dr. Abraham Rabiner, Brooklyn.

Eight cases of infantile amaurotic family idiocy were institutionalized for the major part of their clinical course. These cases displayed all the classical features of Tay-Sachs disease, but in most instances survived for periods beyond that considered representative of the illness. This clinical prolongation was considered a reflection of active nursing care rather than of any inherent variation in the disease. Weekly head-circumference determinations were recorded in all cases. After approximately 18 months of overt illness, rapid cranial enlargement emerged in almost all patients. Multiple pneumoencephalograms disclosed moderate internal hydrocephalus. Review of autopsy material from this actively studied group, and of an additional nine cases with autopsy, showed some correlation between duration of illness and brain weight. Beyond approximately 18 months of recognized illness, brain weights tended to increase above the normal for that particular age. The degree of actual megalencephaly increased in the more protracted cases.

Pathologic studies of the protracted cases showed massive degeneration and demyelination of the cerebral white matter, grossly similar to that in Schilder's disease. The neurocellular damage incident to the dystrophic process resulted in axonal and myelin loss in the underlying cerebral white matter. The increase in brain weight was felt to be a reflection of secondary and exuberant medullary gliosis and massive associated edema. The internal hydrocephalus was attributed to a diffuse meningeal fibrosis incident to the continuous discharge of abnormal lipid components into the subarachnoid space.

DISCUSSION

Dr. Alexander Silverstein, Philadelphia: I should like to express my appreciation for the opportunity of listening to the instructive, stimulating paper by Drs. Aronson and Rabiner. The authors present convincing evidence in a large series of cases of amaurotic family idiocy that there is a correlation of duration of illness to the megalencephaly. This results from a massive degenerative change in subcortical white matter secondary to the neurocellular damage. I have had no personal experience with such cases of megalencephaly in Tay-Sachs disease, nor have I discovered a similar series of cases in the literature.

I should like to ask whether histopathologic studies were made of various viscera, such as pleura, osseous system, liver, and spleen. Chemical analyses of the lipids in various organs would also have been enlightening. Were chemical analyses made of the various organs other than the brain?

Dr. Charles Rupp Jr., Philadelphia: Dr. Aronson and Dr. Rabiner have reported their findings in respect to hydrocephalus and megalencephaly in Tay-Sachs disease. As they point out, their findings are not exactly new, but they have correlated certain facts that have been

scattered in the literature for some time. Lichtenstein states that subsequent to the loss of nerve cells there is a secondary nerve fiber degeneration, which possibly accounts for the diffuse sclerosis found by the authors.

There is possibly another clue as to why these cases resemble Schilder's disease. In the authors' cases there has been a longer survival period than usual, and there has been more time for lipid accumulation to occur. Consequently, demyelination and glial repair with edema have progressed further than usual.

DR. STANLEY M. ARONSON, Brooklyn: As Dr. Rupp stated, the megalencephalic aspects of Tay-Sachs disease are not unique to this presentation.

The question was asked whether or not our cases are actually instances of Tay-Sachs disease, or whether they may perhaps represent some aberrant form related to the juvenile or adult form of amaurotic family idiocy. I wish to reemphasize that all of these cases showed all the classical features which we feel are basic to Tay-Sachs disease. In all cases there was macular degeneration, a finding not generally present in the juvenile form of amaurotic family idiocy. These children would perhaps have died at the anticipated time had it not been for the excellent nursing care they received.

Insofar as the other organs are concerned, with the exception of the two cases of Niemann-Pick disease (with deaths 14 and 15 months, respectively, after the onset of the illness), the organs appeared essentially normal by all histologic and histochemical procedures.

Demyelination and secondary necrobiosis were the most prominent in the cerebral white matter corresponding to cortical areas where diffuse plenary destruction of the neurones was evident. The parieto-occipital and frontal regions showed the most devastating changes.

Supersensitivity of Chronically Isolated and Partially Isolated Cerebral Cortex to Acetylcholine and Other Stimuli As a Mechanism in Focal Epilepsy and in Lobotomy. DR. FRANCIS ASBURY ECHLIN, New York (read by title).

In one series of monkeys, blocks of cerebral cortex were neuronally isolated or partially isolated, and in another series frontal lobotomies were performed. Seven to ten months later 0.2% acetylcholine applied to the cortex caused wave-and-spike discharges selectively from the isolated or the partially isolated areas. Acetylcholine, 0.2% to 0.75%, produced similar discharges selectively from the frontal lobe of the lobotomized animals. The isolated and partially isolated areas were also supersensitive to electrical stimulation and to intravenous pentylenetetrazol (Metrazol).

The findings so far are in keeping with Cannon's law of denervation, providing a plausible explanation of the mechanism underlying focal cortical epilepsy.

Lobotomy causes a profound change in the physiologic chemistry of partially isolated cells (a supersensitivity) in the frontal lobe, and probably elsewhere. It is therefore suggested that the clinical effects of lobotomy are probably, in part at least, the result of this supersensitivity.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Psychiatry and Psychopathology

VISUAL HALLUCINATIONS OF THE SELF IN ORGANIC DISEASE. KENNETH DEWHURST and JOHN PEARSON, J. Neurol., Neurosurg. & Psychiat. **18**:53 (Jan.) 1955.

Dewhurst and Pearson report three cases of autoscopic hallucinations in association with organic disease of the brain. Hallucinations of the self have previously been noted in patients suffering from infectious fevers, particularly typhus, epilepsy, post-traumatic cerebral lesions, and brain tumors. The authors noted similar hallucinations in cases of subarachnoid hemorrhage, a tumor of the parieto-occipital lobe with temporal lobe seeding, and a bullet wound injury of the temporal lobe, respectively. In the first case, autoscopic hallucination was probably provoked by a small vascular lesion of the brain which ruptured and caused subarachnoid hemorrhage. The hallucination was so vivid that upon one occasion the patient drew up a chair for his "double." The second patient had autoscopy in association with a temporal lobe tumor, but he could not recognize himself until the terminal phases of his disease. In the third case, a 13-year period elapsed between the bullet wound injury of the right temporal lobe and the first autoscopic experience.

Although there were many dissimilar features in the histories of the three patients, all had a focal cerebral lesion, and two of the three patients had lesions localized to the temporo-parieto-occipital area. It has been known that, together with cerebral irritation, such variants as visual memory and the degree of visual imagery constitute a subjective basis for hallucinosis. A focal lesion may be the precipitating stimulus that either releases or facilitates the cortical area of recall, which thus presents the autoscopic hallucination to the patient.

MANDEL, Philadelphia.

Physiology and Biochemistry

CEREBRAL COMPLICATIONS FOLLOWING PERCUTANEOUS CAROTID ANGIOGRAPHY WITH CONTRAST MEDIA OF THE DIODRAST GROUP. A. G. FRØVIG and K. KOPPANG, Acta psychiat. et neurol. scandinav. **28**:339, 1953.

Frøvig and Koppang describe the cerebral complications using 35% solutions of compounds of the iodopyracet (Diodrast) group (Uriodone, Umbradil, and Nycotrast) in percutaneous angiography at the University Clinic, Oslo. In 2701 cases only six complications arose. The authors have no pathological data but assume the cause to be changes in vascular permeability and tone. The complications were hemiplegia in five cases and homonymous hemianopsia in one, the most short-lived, except in one older patient, in whom sequelae still remained after several months. The authors conclude that this small incidence should not deter one from using 35% iodopyracet (Diodrast) provided one adheres to the tenets laid down by Broman and colleagues, namely, intervals of at least 15 minutes between repeated injections and use with care in cases of patent vascular injury and certain cerebral diseases.

BERRY, Philadelphia.

Neuropathology

UNUSUALLY SEVERE LESIONS IN THE BRAIN FOLLOWING STATUS EPILEPTICUS. A. MEYER, E. BECK, and M. SHEPHERD, J. Neurol., Neurosurg. & Psychiat. **18**:24 (Jan.) 1955.

The authors report the changes in the brain of a 9-year-old child who had an episode of status epilepticus without any apparent reason while being treated for Still's disease (multiple rheumatoid arthritis). This seizure was followed by unconsciousness for a three-day period, and then pneumonia. Upon recovery the child was found to be severely demented. He then had grand mal, petit mal, and temporal lobe seizures until his death, which occurred one year after the onset of the attacks.

Gross examination of the brain revealed definite symmetrical atrophy of the entire brain, most marked over the temporal lobes. There was symmetrical enlargement of all ventricles. The amygaloid nucleus was degenerated in its ventral aspect. The cerebellum showed atrophy of several lobules, particularly near the central white matter.

Microscopic examination revealed focal lesions in the Sylvian region, inferior frontal convolution, superior temporal convolution, cornu ammonis, anterior cingulate region, and insula. In these areas there was an almost complete loss of neurons, with an increase in microglia cells. Endothelial proliferation was prominent, and there was proliferation of the fibrous glia from the marginal layer to the third layer, which revealed a laminar loss of neurons. Sclerosis was present in Sommer's sector of the cornu ammonis. The amygdaloid nucleus in its ventral aspect revealed extensive glial and mesodermal proliferation. Areas of degeneration were also noted in the anterior and lateral nuclei of the thalamus.

These changes in the temporal lobe in status epilepticus are the same as those described by other observers in birth injuries of the temporal lobe, with herniation of the uncus and anoxia. The bilateral softening in the amygdaloid nucleus was found for the first time in an epileptic brain, and, in subsequent studies by the authors, it was found that amygdaloid nucleus degeneration was associated with sclerosis of the cornu ammonis and the uncus. It is thought that the cornu ammonis and the amygdaloid nucleus have a role in epileptic discharge and that these centers in a situation of anoxia would be more susceptible and thus degenerate.

MANDEL, Philadelphia.

SOME HISTOLOGIC AGE CHANGES IN THE RAT'S BRAIN AND THEIR RELATIONSHIP TO COMPARABLE CHANGES IN THE HUMAN BRAIN. H. KUHLENBECK, Confinia neurol. **14**:329-342, 1954.

Kuhlenbeck reports a histologic study of a series of Wistar Institute rats ranging from birth to old age and compares the findings with experience in human material.

In the larger cerebral arteries of old animals the elastica interna appeared thinner, stained less well with elastin stain, and seemed to have lost some of its elasticity. The intima showed occasional, but very conspicuous, scattered circumscribed swellings, which appeared to result from one or two large, hyperplastic subendothelial cells surrounded by a small amount of amorphous granular material. The media showed degenerative changes characterized by frequent, isolated large vacuoles and by replacement of smooth muscle with fibrous connective tissue. The arterioles of old animals showed changes varying from thickening of all layers to a structureless hyaline wall.

The leptomeninges of old animals were increased in thickness, and the leptomeningeal vascular prolongations into brain tissue showed a similar change.

The nerve cells of the cerebral cortex in the aged rats showed "various degrees of pyknosis and shrinkage, including in some instances patchy areas of apparently complete cell loss. Some of the pyramidal cells showed the picture of so-called chronic cell disease which cannot be clearly distinguished from that of ischemic cell change."

Most old animals displayed definite neurofibrillar changes. The neurofibrils appeared clumped together, and thickened, with varicosities, and with thick, fused strands running adjacent to the surface of the cell. Typical whorls, intraneuronal tangles, and basket formations were not found. A determined search for alterations corresponding to senile plaques was undertaken with various techniques, but with negative results.

FOLEY, Boston.

Diseases of the Brain

TUMORS OF THE PINEAL REGION. N. RINGERTZ, H. NORDENSTAM, and G. FLYGER, J. Neuropath. & Exper. Neurol. **13**:540 (Oct.) 1954.

Sixty-five pathologically verified tumors in the pineal region (excluding meningiomas and angiomas) were studied. Of these, 14 belonged to the glioma-neuroblastoma group, 38 were pinealomas and teratomas, 11 were undifferentiated tumors (the spongioblastic pinealoma of Horrax and Bailey), and 2 were non-neoplastic pineal cysts.

The pinealomas were divided into three histologic subgroups: (1) seminoma-like tumors, (2) the ordinary two-cell-patterned type, and (3) the adult type, resembling the adult pineal body. Transitions between these groups were observed. Of the 11 teratomas, 6 showed evidence of pineal tissue.

Neurologic symptoms were commonly those of increased intracranial pressure and the ophthalmological abnormalities pointing to a quadrigeminal-plate lesion.

In the present series the treatment generally consisted of radical removal of the primary growth and postoperative x-ray treatment. About 40% of patients survived the operation. Seven with tumors belonging to the histologic group of undifferentiated pinealoma-teratoma lived over five years.

SIEKERT, Rochester, Minn.

DECEREBRATE STATE IN CHILDREN AND ADOLESCENTS. ROBERT C. L. ROBERTSON AND CLAUDE POLLARD JR., J. Neurosurg. **12**:13, 1955.

The clinical signs of decerebrate rigidity are seen frequently in humans as a result of traumatic or vascular lesions. The characteristic neurologic signs of profound unconsciousness, pinpoint pupils, extensor rigidity in the arms and legs, and bilateral Babinski sign are indicative of a severe lesion at midbrain level, which is associated with a more or less hopeless prognosis.

The authors report 13 unselected cases of decerebrate rigidity from varying causes with ages ranging from 2 to 57 years and found that the children in this group who were able to survive the immediate decerebrate state had a much better prognosis than the adult. Six of the 13 children and adolescents are relatively normal neurologically, as compared with none of the 13 adults who showed similar decerebrate states. However, the initial mortality of the decerebrate state in children is probably higher than in adults. Tracheotomy is advocated as an early measure to control respiratory obstruction secondary to secretions, which may lead to hypoxia and increase the neurologic deficit.

MANDEL, Philadelphia.

PTERIONAL MENINGIOMA "EN PLAQUE": REPORT OF A CASE OF 36 YEARS' DURATION. KENNETH H. ABBOTT and BERNARD GLASS, J. Neurosurg. **12**:50, 1955.

Abbott and Glass report the case of a 59-year-old white woman who had a history of proptosis of the right eye with progressive loss of vision, ophthalmoplegia, and facial disfigurement. This patient was thought to have had an inoperable tumor when she was first seen, in 1916; hence, no surgical intervention was attempted. However, when her symptoms became progressively worse, she was studied and found to have a meningioma extending from the sphenoidal ridge into the middle fossa to the petrous bone. A major part of the tumor was removed, and the orbit was decompressed. The proptosis was reduced, and the patient's general condition was improved. Microscopic examination of the tumor revealed it to be a meningioma.

MANDEL, Philadelphia.

SOME OBSERVATIONS ON THE ELECTROENCEPHALOGRAM IN CEREBRAL TUMORS. J. H. D. MILLAR, J. Neurol., Neurosurg. & Psychiat. **18**:68 (Jan.) 1955.

Brain tumors are electrically inert, but the slow waves which are present in the EEG in association with brain tumor are due to the partially damaged surrounding tissue. Increased intracranial pressure may produce slow activity. Millar states that in supratentorial lesions this rise is the result of cerebral edema, and in infratentorial lesions, of active dilatation of the ventricles. Infiltrative supratentorial tumors, even when extensive, may cause little or no mechanical or metabolic disturbance of normal cells, so that slow activity does not result; and thus a normal electroencephalogram should not mislead the clinician in the presence of other evidence of tumor. The EEG in subdural hematomas was of little lateralizing value in his series of five cases.

MANDEL, Philadelphia.

SOME CLINICAL FEATURES OF THE SYMPTOMATOLOGY OF GLIOMAS OF THE TEMPORAL LOBE. JENS EDMUND, Acta psychiat. et neurol. scandinav. **39**:311, 1954.

Edmund reports the clinical features encountered in 196 verified cases of glioma. Astrocytomas occurred most frequently in this series, followed in incidence by glioblastoma multiforme. The author included glioblastomas and medulloblastomas in the malignant group, while astrocytomas, ependymomas, oligodendrogliomas, and spongioblastomas comprised the benign group of gliomas.

Papilledema, hemiparesis, memory disturbances, and aphasia occurred with much greater frequency in the malignant than in the benign group. Hallucinations of smell and taste were also found to occur approximately twice as frequently in the malignant group. Convulsive seizures,

uncinate fits, and dreamy states occurred with greater frequency in the benign gliomas. Two-thirds of the malignant gliomas occurred in male patients, while only one-half of the more benign gliomas arose in male patients. The malignant tumors appeared approximately 20 years earlier than in female patients, and approximately one-half of the gliomas in the male patients were glioblastomas.

MANDEL, Philadelphia.

Encephalography, Ventriculography and Roentgenography

VENOGRAPHHIC CLUES TO LOCALIZATION OF INTRACRANIAL MASSES. P. A. REIMENSCHNEIDER and A. ECKER, Am. J. Roentgenol. **72**:740 (Nov.) 1954.

Reimenschneider and Ecker expose films four to six seconds after arterial filling in cerebral arteriograms in order to obtain filling of the cerebral veins. The authors discuss and illustrate the normal findings in cerebral venography and state that the deep veins of the brain form such a constant pattern that certain deviations from the normal can be interpreted as significant. The normal locations are described for the internal cerebral vein, the vein of the septum pellucidum, the thalamostriate vein, the choroidal vein, the great vein of Galen, and the basilar vein of Rosenthal.

In suprasellar tumors upward displacement of the basilar vein of Rosenthal is likely to be found. Often this vein presents an appearance which suggests that it is stretched. Frontopolar tumors regularly show downward and backward displacement of the origin of the internal cerebral vein and the foramen of Monro. Downward displacement of the vein of the septum pellucidum and the thalamostriate vein often accompanies the displacement of the internal cerebral vein. Tumors in the region of the caudate nucleus and thalamus elevate the thalamostriate vein and displace the foramen of Monro downward and backward. Occasionally the vein of Rosenthal is displaced backward and downward. Large parietoparasagittal tumors might be expected to flatten the vein of Galen. Tumors invading the splenium of the corpus callosum produce a ballooning effect on the vein of Galen. This ballooning provides an important clue to the inoperability of the tumor.

The findings of displacement of an anterior cerebral artery across the midline and separation of small branches of the middle cerebral artery from the inner table of the skull have long been recognized as important in the diagnosis of subdural hematoma. Frequently the venogram will demonstrate displacement of veins from the inner table of the skull more vividly than the arteriogram demonstrates the displacement of arteries. Thus, the size and shape of the hematoma can often be more accurately outlined on the venogram. Tumors of the middle and posterior portion of the temporal lobe cause an upward displacement of the ampulla of Galen. Elevation of the vein of Labbé has been seen also. Cerebellopontine-angle tumors produce changes similar to those produced by masses in the temporal lobe, but the elevation of the basilar vein is diffuse and accompanied by stretching of the vein rather than a localizing humping. Pineal tumors often produce an upward convexity in the curve of the vein of Galen.

WEILAND, Grove City, Pa.

SOME COMPLICATIONS OF VERTEBRAL ANGIOGRAPHY. OSCAR SUGAR and PAUL BUCY, J. Neurosurg. **11**:607, 1954.

Sugar and Bucy report three cases of complications during vertebral angiography. Death occurred in two of the cases as a direct result of angiography, which was performed with iodopyracet (Diodrast) with the patient under general anesthesia. The third case recovered after she had shown a progression of symptoms. In each case the angiogram revealed arteriosclerosis of the vertebral basilar system.

The authors reemphasize the hazards encountered with acetrizoate (Urokon) and Diodrast during cerebral angiography. They believe that complications of vertebral arteriography under general anesthesia may be reduced by limiting the number of injections and the amount of contrast medium used, as well as by lengthening the interval between injections. The common factor in these cases was atherosclerosis, with narrowing of the lumen of the major vessels in the vertebral and basilar systems, and the injected Diodrast could cause enough internal swelling to occlude the already narrowed vessel. If the arteriography is done with local anesthesia and the patient shows any untoward effects, such as coma, hemiplegia, or hemianopsia, the procedure should be discontinued.

MANDEL, Philadelphia.

TOTAL MYELOGRAPHY. J. T. BRIERRE and J. A. COLCLOUGH, Radiology **64**:81 (Jan.) 1955.

Brierre and Colclough perform myelography by injecting 21 cc. of ethyl iodophenylundecylate (Pantopaque) into the subarachnoid space in the lumbar region. They withdraw fluid for laboratory examination but do not attempt to withdraw 21 cc. before injecting the 21 cc. of Pantopaque. After the injection of the Pantopaque, the needle is removed from the spine and the patient walks about the room for a while. The lumbar subarachnoid space is studied by erect films. The patient then lies supine, and in this position the entire thoracic portion of the subarachnoid space can be studied by means of films. Finally, the patient is placed in the prone position; the head is elevated, and the table is placed in the Trendelenburg position in order to fill the cervical portion of the subarachnoid space without running the contrast material up into the head.

The authors believe that the method offers a quick way of obtaining myelograms and offers a good method by which to study the entire spinal canal myelographically. There is less handling of the patient, and the study can be performed in less time. A lumbar puncture is necessary after the films have been made, in order to remove the contrast material. The authors state that the contrast material seems easier to remove when used in large quantities than when the usual small amount is used. They also feel that this method probably is more accurate than the methods which use 3 to 6 cc. of the contrast material. They believe it is unlikely that a herniated intervertebral disc will not be seen, if present, when one uses this method. They have examined 18 patients in this manner and have operated upon 15 of the 18. They have found no false-positive or false-negative results in this small series of cases.

WEILAND, Grove City, Pa.

THE DIAGNOSTIC VALUE OF THE DEEP CEREBRAL VEINS IN CEREBRAL ANGIOGRAPHY. B. S. WOLF, C. M. NEWMAN, and B. SCHLESINGER, Radiology **64**:161 (Feb.) 1955.

A study of the deep cerebral veins by taking films four to six seconds after the injection when performing internal carotid angiography provides important additional information and supplements the study of the position of the cerebral arteries during this procedure. Wolf, Newman, and Schlesinger take seven serial films in eight seconds, in order to allow for those persons with increased intracranial pressure in whom the cerebral circulation may be slower than normal. The article concerns itself mainly with various displacements of the internal cerebral veins. There are two internal cerebral veins. Each is formed approximately at the interventricular foramen by the union of the septal, anterior caudate, posterior caudate, and terminal veins. The internal cerebral veins run backward, parallel with each other, just lateral to the midline, between the layers of the tela chorioidea of the third ventricle and beneath the splenium of the corpus callosum. Both internal cerebral veins unite in the midline to form the great cerebral vein of Galen in the cisterna ambiens. In the lateral view of the skull the junction of the internal cerebral vein with the great vein of Galen cannot be identified; so the authors find it convenient to refer to both the internal cerebral and the great vein by the single designation "the deep vein of the brain."

The posterior portion of the deep vein of the brain rarely shows displacement, since the vein of Galen empties into the straight sinus and the insertion of the falx in the tentorium at this region is relatively rigid. In gross displacements of the deep vein of the brain the internal cerebral vein pivots around this fixed point. Changes in shape and position of the internal cerebral vein can be divided into two general groups: (1) those with obvious distortion of the vein, and those with en bloc displacement of the vein without local distortion. The lesions which produce local distortion of the vein are those which are located immediately adjacent to it, that is, primarily central lesions. Lesions of the corpus callosum, the thalamus, and the third ventricle may produce local distortions of the vein. Large lesions of the anterior fossa may cause posterior displacement of the deep vein and give it the appearance of a tense spring, with an exaggeration of the normal curves. Lesions above the sella turcica produce elevation of the anterior portion of the vein. Deep parietal lesions produce a widening and flattening and gentle downward convexity of its descending portion. Parasagittal neoplasms of large size produce a flattening of the adjacent portion of the vein over a considerable portion of its length. Moderate elevation and medial displacement of the vein are seen in some temporal lobe tumors.

The authors have devised a system of measurements for the position of the deep vein of the brain in an effort to detect small deviations from normal. The obviously abnormal is easily detected upon inspection of the films; but if minimal abnormalities can be detected, the method

should produce a higher percentage of accurate diagnoses. The authors select three easily located points on the deep vein of the brain, as seen in the lateral projection of the skull. They draw an arbitrary line between the tuberculum sellae and the inferior margin of the sulcus for the transverse sinus in the middle portion of the occipital bone. Measurements are made from this base line both to the three preselected points on the deep vein and to three points on the inner table of the skull. The ratio of the distance from the base line to the vein and the base line to the inner table of the skull has been determined in normal persons and is used for guidance in locating the expected normal path of the vein through the brain. Since the deep vein of the brain has a relatively constant location within the cranial cavity of normal persons, varying only with the size and shape of the skull, the authors believe that it is possible to predict the normal position of the three selected points along the vein within 3 or 4 mm.

WEILAND, Grove City, Pa.

THE ROENTGENOGRAPHIC DIAGNOSIS OF THE ARNOLD-CHIARI MALFORMATION. R. SHAPIRO and F. ROBINSON, Radiology **64**:390 (March) 1955.

The Arnold-Chiari malformation is a downward transposition of the cerebellum and medulla to the cervical portion of the spinal canal. Shapiro and Robinson report the myelographic findings in a case of the malformation which they have seen and compare them with myelographic findings in two cases of cervical meningioma. All three cases presented a somewhat similar clinical picture, consisting of the symptoms and signs of cord compression high in the cervical region. Shapiro and Robinson believe that in the pure, uncomplicated Arnold type of malformation cervical myelograms should demonstrate an obstructive cervical lesion with an inferior bilobulated border, which is caused by the inferior margin of the herniated cerebellar hemispheres. However, since dense adhesions are frequently present over the cord in association with the Arnold-Chiari malformation, one cannot depend on demonstrating the typical picture. The combined Arnold-Chiari deformity results in buckling and downward displacement of the medulla against the cervical cord. The pressure of the medulla may cause a complete block of the opaque myelographic medium, and the typical bilobulate pattern produced by the herniated cerebellar hemispheres may not be seen. The differential roentgen diagnosis of these defects in the myelograms of children and adolescents is not difficult, because high spinal cord tumors in this age group are uncommon. The coexistence of such a myelographic finding with hydrocephalus favors the diagnosis of the Arnold-Chiari malformation. In adults the problem is much more difficult, since many other diseases must be considered in the differential diagnosis.

WEILAND, Grove City, Pa.

COMPARATIVE STUDIES OF DISCOGRAPHY AND MYELOGRAPHY. J. WOLKIN, M.D. SACHS, and G. H. HOKE, Radiology **64**:704 (May) 1955.

Wolkin, Sachs, and Hoke performed in a series of cases lumbar discograms after the method of Lindblom. In this method the intervertebral disc spaces are injected directly with iodopyracet (Diodrast). The authors injected the discs between the fourth and the fifth lumbar vertebra and between the fifth lumbar vertebra and the sacrum. The injection of these two discs is a routine with most workers who have tried the method.

The authors report a series of 27 patients who were selected consecutively from a larger group. Each patient represented, in the opinion of the authors, a clear-cut clinical example of herniation of a lumbar intervertebral disc. In the majority of the cases neither lumbar myelography nor discography was considered necessary for the diagnosis. Of the 27 patients, 26 underwent lumbar laminectomy and exploration. One patient with a normal discogram was not operated upon; autopsy later proved that he had no herniated disc but that he had bone metastasis from a primary adrenal tumor. In 18 of the 27 patients both myelography and discography were performed. In nine patients only discography was performed.

Wolkin, Sachs, and Hoke believe that discography is a more accurate procedure than myelography in the diagnosis of herniated intervertebral disc. They consider a normal discogram as very strong evidence that there is no abnormality of the disc, whereas a negative myelogram does not rule out a herniated intervertebral disc. Unsuspected multiple herniations were found more frequently by discography than by myelography. Information concerning degeneration of the intervertebral disc without herniation can be obtained by this method. The time of examination is short, since the contrast material need not be removed after the examination, and no contrast material enters the subarachnoid space, to cause irritation there. The disadvantages

of discography, when compared with myelography, are (1) the possibility of injuring the annulus fibrosus when introducing the needle, and thus producing a herniated intervertebral disc through the site of injury, and (2) the limitation of the procedure to the diagnosis of intervertebral disc lesions in the lumbar area. Myelography can be used to study the entire spine, and the different levels are studied with a great deal more ease.

WEILAND, Grove City, Pa.

RADIOLOGICAL APPEARANCES OF AGENESIS OF THE CORPUS CALLOSUM. P. SHELDON and A. PEYMAN, J. Neurol., Neurosurg. & Psychiat. **16**:117 (May) 1953.

Two cases of agenesis of the corpus callosum are reported. From a review of the literature it seems that the most frequent symptoms of this condition are epilepsy and a varying degree of mental impairment. The former symptom was present in both the cases reported in this paper, and both showed slight lateralizing signs, but no evidence of mental impairment in either case. The roentgenologic appearances of agenesis of the corpus callosum are reviewed. In both these cases all the criteria of Davidoff and Dyke (1943) were found, with the exception of the radiate pattern of the medial cerebral sulci.

The appearances seen in carotid angiograms in this condition have not previously been reported. In the two cases presented the angiograms showed signs which are probably diagnostic. The position and course of the anterior cerebral artery were unusual and reflected the absence of the corpus callosum. In one case the anterior cerebral artery followed a very irregular, wavy course in the anteroposterior veins, possibly due to absence of "splinting" by the corpus callosum, but it did not cross the midline. In the second case the artery ran a much straighter course in the anteroposterior vein.

The internal cerebral vein lay higher than usual and was also above the roof of the third ventricle. The normal curve of the great cerebral vein was greatly diminished and was situated above and in front of its usual position.

The authors consider carotid angiography as an aid in diagnosis of this condition.

ALPERS, Philadelphia.

BASILAR IMPRESSION. D. G. PHILLIPS, J. Neurol., Neurosurg. & Psychiat. **18**:58 (Jan.) 1955.

Phillips reviews the problem of establishing the lower limit of abnormality in basilar impression by roentgenogram, although there are various radiological criteria which identify the typical case.

Basilar impression is congenital or acquired, and the acquired form is most frequently associated with Paget's disease (osteitis deformans) of the skull. There is also a high incidence of developmental anomalies associated with basilar impression, consisting of midline cranial defects, fused cervical vertebrae, bifid cervical arch, anencephaly, harelip, stenosis of the aqueduct, and cerebral aneurysm (in one case of the author's series).

The author reports the clinical findings in 12 cases, the ages ranging from 8 to 60 years. The symptoms and signs were due to hydrocephalus, cranial nerve disorders, cerebellar dysfunction, and interference with long tracts. Suboccipital pain and headache were prominent features of basilar impression. Changes in posture frequently aggravated the headache. Cerebellar signs included ataxia and nystagmus. A short, flattened neck was not obvious in most of the cases, although dorsal kyphosis and increased cervical lordosis were frequently observed. Sensory findings were variable. Spinal fluid findings revealed protein levels of 15-70 mg. per 100 cc. in all but two cases, where partial or complete block was present, in which cases the levels were 150 and 500 mg. per 100 cc., respectively.

Surgical treatment was required when a neurological syndrome was progressive. Special difficulties arose in the postoperative management of these cases, due to disorders in the medulla, respiratory tract, and pleocytosis of the spinal fluid, with persistent reaccumulation of fluid.

MANDEL, Philadelphia.

Books

Clinical Neurosurgery. Proceedings of the Congress of Neurological Surgeons. Vol. 1. Price, $8.00. Pp. 201, with 89 figures and 11 tables. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

Sir Geoffrey Jefferson was the guest of honor at this New Orleans Congress in 1954 and contributed three remarkable papers, as follows: (1) Changing Views on the Integration of the Brain; (2) Trigeminal Neuromas with Some Remarks on the Malignant Invasion of the Gasserian Ganglion; (3) Further Remarks Concerning Compression of the Optic Pathways by Intracranial Aneurysms. These scholarly essays reveal vast acquaintance with the literature; and deft touches here and there serve to make the reader sit up and take notice—for instance, "The foregoing account of the sparse literature on the subject of aneurysms of the ophthalmic artery might well induce the reader to think that these lesions, so common inside the skull, must be just about as common as mermaids."

The other half of the book is devoted to three panel discussions: (*a*) Anatomy and Physiology of the Frontal Lobe; (*b*) Psychosurgery—Indications and Sequelae; (*c*) Use of Fluids and Electrolytes in the Management of the Neurosurgical Patient. Brief summaries of current knowledge concerning the phylogenetic development of the frontal lobes by von Bonin, metabolic considerations by Himwich, and the structural basis for functioning of the frontal lobes by Walker usher in Heath's description of an interdisciplinary approach to the understanding of mind-brain relationships. Walker's description of colonies of monkeys who had undergone frontal lobectomy or temporal lobectomy is very apposite. "Now if we take off the frontal lobe of all those members, the hierarchy remains. Oh, the king may be a bit more arrogant and a bit nastier to each of the members below him, but nevertheless he is still king. There is no question about that. On the other hand, if we remove the tip of the temporal lobes, the day after operation the animal walks out of his cage, looks at the observer with no sign of fear or aggression, and the behavior of this animal with reference to the remainder of the colony is changed entirely. He who was king before the lobectomy may now be picked upon by all members and assume the lowest rank in that colony. Some other member of the colony will then assume kingship. In other words, although there is a certain apathy produced by both frontal and temporal ablations, in the case of the temporal lobectomized animal, there is a definite change in the animal's reaction to its social environment, whereas the frontal lobectomized animal has lost its internal tensions, but is still well oriented to its external milieu."

Heath's experiments in stimulation of the septal region have been described in his recently published monograph.

A review of the rationale of frontal lobe operations by von Bonin tends to assign different functions to different parts of the frontal lobes. Thus, the inner surface, and particularly the cingulate area, appears to be a strong suppressor area, and operations here tend to render the individual asocial but more docile and fearless. The author believes that the convexity is more concerned with forecasting the future of events in the external world, while the orbital area, the end station of the vagus, apparently has to do with impulses arising within the individual himself. Working with topectomy, however, Pool could find no differences in the effects of equal ablations from the medial, basal, and convex surfaces of the frontal lobes. The deleterious effects of major prefrontal lobotomy, according to both Heath and Pool, have led to the development of a number of selective operations. According to the latter, "The point is that with limited procedures, whether lobotomy or topectomy, drive need not necessarily be restricted or social activities or interests be reduced." The incidence of epilepsy following major frontal operations was considerable, ranging from 10% to 80% in several series. Stimulation of the cortex during operation raised the percentage of convulsive cases. Heath was asked what were the effects of lobotomy on the psychosis itself, and replied: "I think I can confidently state that the destructive cortical operations have no effect whatsoever on the psychosis. I am referring now to the basic psychotic process, and do not mean to imply that there is no symptomatic improvement in the overall social adaptation of the patients." Pool, however, pointed out that in many instances in which psychotic deterioration had not occurred, there was progressive improvement in the patients in the years following operation. This discussion led to a consideration of the indications for

psychosurgery, with more emphasis than usual upon painful conditions. Freeman reported a study of 2000 operations—one-third prefrontal lobotomies; two-thirds transorbital lobotomies. Deaths were twice as frequent in the prefrontal series, and complications and sequelae twenty times as common. He stressed the greater safety of the transorbital lobotomy, which he called the Model T, or poor man's, lobotomy. Asked a pointed question, Pool stated that he saw "no reason why we neurosurgeons shouldn't do the transorbital lobotomy."

Heath found many contraindications to lobotomy, considering it merely palliative treatment. "I believe that the data we have gathered through psychosurgical procedures should be used as a stepping stone towards the development of more effective methods and should not be considered as treatment in itself." Experiences with unilateral lobotomy have been disappointing, likewise with intrafrontal injection of procaine. Walker closes with an eloquent plea for further research in the whole field. "But let the psychosurgeon not forget that the real secret he seeks lies not in the dissolution of the brain, be it by scalpel, icepick, electrocoagulation, gamma, or supersonic ray, but in the integration of the nervous system. Not by encephalopathy but by encephalization man developed from his savage ancestors. Rather than seeking ways to decrease man's over-perfectionistic desires, we might devote more time, energy and research to develop means by which the quality of the nervous system might be improved so as to be able to overcome the stresses to which it is subjected by our present social order. This is not impossible of achievement by the cooperative efforts of the biochemist, biophysicist, and physician. Then the era of psychosurgery will have passed. But until that time we shall probably go on mutilating brains to bring boasting Cesars and weeping Cleopatras—not to their right senses—but to a less obnoxious and less obvious psychotic state."

Primera Conferencia Méxicana de Neurología Quirúrgica y Psico-Cirugía. Edited by M. Velasco-Suárez and J. Sánches Burciaga. Price, not given. Pp. 183. Editorial Progreso, S. A., México, D. F., Mexico, 1954.

In connection with the tenth surgical assembly of Mexico in November, 1952, a conference on neurological surgery and psychosurgery was held under the honorary presidency of Freeman and Watts. The editors have collected as many of the papers as were available, but without the accompanying discussion. In discussing the future of psychosurgery, Freeman stressed the riddle of the anatomically normal brain in the presence of advanced schizophrenic deterioration and expressed the thought that some means might be found to restore the brain to effective functioning. One of the pressing problems was a more effective treatment of hallucinations, and in this respect the temporal lobe seemed to offer a more promising field of endeavor. Difficult problems of uncontrollable alcoholism, criminality, drug addiction, and psychopathy seemed as far as ever from solution, although in cases of sexual psychopathy there was a ray of hope. The problem of presenting the results in such a manner as would convince skeptics seemed to lie in the field of the psychologist working with patients in whom psychotic deterioration had not occurred before operation.

Velasco-Suárez focused attention on the temporal lobes and the amygdaloid nuclei, particularly in the treatment of psychomotor epilepsy, but found some beneficent results in patients with hallucinations associated with organic disease of the brain. The results of amygdaloidectomy in schizophrenics with hallucinations were much less satisfactory.

Watts reported his experiences in 43 patients treated by lobotomy for the relief of unbearable pain. In this thoughtful article, he stressed "the limitations and risks of psychosurgery because the surest way to throw a method of treatment into disrepute is to claim for it more than it can deliver. Lobotomy does relieve some types of pain; it does not relieve other types. The effects of lobotomy on the personality of pain patients is often grave and must be weighed against the relief which may be expected from operation." Of the survivors, 57% experienced great relief of pain, and an additional 23% were partially relieved. Some of the patients required a second operation. The standard operation brought the most consistent relief, while section of the lower quadrants was superior to either transorbital lobotomy or unilateral lobotomy. Exclusive of the cancer patients whose expectation of life was short anyhow, the authors studied 18 patients, with other painful conditions, over a period of one to seven years. Here the suffering was greatly or partially relieved in 16. However, only one patient was employed, three were keeping house, and six patients who had not previously been hospitalized required confinement in mental institutions because of the development of irresponsible or aggressive behavior. In this connection, Watt discussed the effect of lobotomy on the attitude of he family. Citing two

characteristic vignettes, he showed that when the patient was no longer suffering, but was merely dictatorial, the attitude of the family underwent a corresponding change. As far as mechanisms of pain relief are concerned, Watts agreed with Koskoff that lobotomy is effective in the relief of suffering, and with Scarff that lobotomy is a relative barrier between pain reception and pain perception at the conscious level. He concluded that since the price of lobotomy is so high in terms of later social adjustment, "the risks must be carefully weighed against the relief that may be expected. . . . the present trend is toward selective types of operations which cause less damage to the personality."

In a brief summary, Kenneth Livingston reported experiences with 58 chronic schizophrenic patients treated by anterior cingulectomy and followed from six months to three and a half years. Twenty-one of these patients were out of the hospital for six months or more, and several of them were employed.

Obrador Alcalde and Sánchez Juan studied the psychic symptomatology of 124 patients undergoing extensive or partial ablation of various areas of the brain for removal of tumors and other pathologic lesions. No significant psychiatric abnormalities followed removal from the parietal, central, or occipital areas. Partial frontal lobectomy was more apt to cause symptoms when it was performed on the left side than on the right. However, the discrepancy was much more marked in connection with temporal extirpations.

Barahona Fernandes compared the hyperpathia syndrome found in lesions of the thalamus and parietal areas with the hypopathia after frontal lesions. In the former there is reduction in cutaneous sensibility with exaggerated emotional response, whereas in the frontal syndrome there is increased reaction to cutaneous stimulation but decreased emotional response. He concluded that frontal connections are important in the maintenance of internal sensibility "and especially in its higher integration in the ego and in its relationship with external sensibility." The author called attention in this connection to the concept of the visceral brain, with particular reference to the orbital and cingular areas.

Several other essays review the general situation with regard to neurosurgical and psychosurgical problems.

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Lehmann, H.E.: Canad. M. A. J. 72:91
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